



FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform

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FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform

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Abstract

On December 14, 2006, FDA proposed two new regulations in the Federal Register amending current regulations governing expanded access to investigational drugs for treatment use and charging for investigational drugs. The proposal comes at a time when FDA has been under new pressure to provide seriously ill patients with early access to investigational drugs outside the framework of clinical trials. In recent years, patient advocacy groups have filed citizen petitions with FDA asking the agency to provide specific criteria for obtaining access or to create an early approval mechanism to provide access. Further, FDA has seen proposed federal legislation intended to ensure early patient access to investigational treatments and nearly lost a lawsuit in federal court in which terminally ill patients sought a fundamental right of access to investigational therapies under the Due Process Clause of the Constitution.

The proposed regulations seek to assuage patient activists, physicians, drug sponsors, and other critics who contend that FDA must strike an appropriate balance between allowing patient access to promising treatments while protecting against undue risks and safeguarding the clinical trials process. Although FDA heralded the announcement of the rules as a key step forward to improving patient access, the proposal fails to expand access beyond measures currently available under longstanding agency practice and, in fact, creates additional regulatory barriers and disincentives for industry participation in expanded access programs.

This paper examines the proposal in light of historical agency regulation and recent pressures to expand access. Section II describes the historical development of FDA's statutory authority to regulate drugs and the traditional new drug approval process. Section III describes the various methods through which FDA has allowed expanded access to investigational treatments since 1962. Section IV recounts various recent pressures on FDA to reform its expanded access procedures and describes the context in which FDA's recent proposal has arisen. Section V details the changes proposed in both the proposed rules to expand access to investigational treatment and charging for investigational drugs. Section VI evaluates the proposed regulations and argues that the proposal is likely to *decrease* access for patients because new restrictions on charging provide no incentive for industry participation and the proposed regulations create increased regulatory barriers to access inconsistent with FDA's statutory mandate.

FDA's Proposed Regulations to Expand Access to Investigational Drugs for Treatment Use: The Status Quo in the Guise of Reform

I. INTRODUCTION

On December 14, 2006, FDA proposed two new regulations in the Federal Register amending current regulations governing expanded access to investigational drugs for treatment use¹ and charging for investigational drugs.² The proposals come at a time when FDA has been under new pressure to provide seriously ill patients with early access to investigational drugs outside the framework of clinical trials. In recent years, patient advocacy groups have filed citizen petitions with FDA asking the agency to provide specific criteria to patients and sponsors seeking expanded access or to create an early approval mechanism to permit easier access to investigational therapies. Further, FDA has seen proposed federal legislation intended to ensure early patient access to investigational treatments and nearly lost a lawsuit in federal court in which terminally ill patients sought a fundamental right of access to investigational therapies under the Due Process Clause of the Constitution.³

The proposed rules seek to assuage patient activists, physicians, drug sponsors, and other critics who contend that FDA must strike an appropriate balance between allowing patient access to promising treatments while protecting against undue risk and safeguarding the clinical trials process. Although FDA heralded the announcement of the rules as a key step forward to

¹ Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75147 (proposed Dec. 14, 2006) (to be codified at 21 C.F.R. pt. 312) [hereinafter Proposed Rules to Expand Access].

² Charging for Investigational Drugs, 71 Fed. Reg. 75168 (proposed Dec. 14, 2006) (to be codified at 21 C.F.R., pt. 312) [hereinafter Proposed Rules for Charging].

³ See *infra*, Section IV, notes 211 to 270 and accompanying text.

improving patient access,⁴ the proposal does not expand access beyond measures currently available under longstanding agency practice and, in fact, creates additional regulatory barriers and disincentives for industry participation in expanded access programs.

This paper examines the proposal in light of historical agency regulation and recent pressures to expand access. Section II describes the historical development of FDA's statutory authority to regulate drugs and the traditional new drug approval process. Section III describes the various methods through which FDA has allowed expanded access to investigational treatments since 1962. Section IV recounts various recent pressures on FDA to reform its expanded access procedures and describes the context in which FDA's recent proposal has arisen. Section V details the changes proposed in both the proposed rules to expand access to investigational treatment and charging for investigational drugs. Section VI evaluates the rules and argues that the proposal will fail to expand access for patients because new restrictions on charging provide no incentive for industry participation and the proposed regulations create increased regulatory barriers to access inconsistent with FDA's statutory mandate.

II. HISTORICAL DEVELOPMENT OF FDA'S STATUTORY AUTHORITY

A. The Pure Food and Drugs Act of 1906

The first chapter of federal food and drug regulation begins in 1906⁵ when Congress enacted the Pure Food and Drugs Act ("1906 Act").⁶ The 1906 Act, which was intended to

⁴ See Press Release, FDA Proposes Rules Overhaul to Expand Availability of Experimental Drugs (Dec. 11, 2006) *available at* <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01520.html>.

⁵ Although Congress had enacted various drug regulation statutes during the 19th century, the Pure Food and Drugs Act of 1906 can fairly be described as the birth of the modern era of food and drug regulation. For a discussion of the first drug regulation in the United States, see Wesley J. Heath, *America's First Drug Regulation Regime: The Rise and Fall of the Import Drug Act of*

address concerns over widespread adulteration and impurity in food and drugs, imposed a variety of labeling and disclosure requirements on drug manufacturers.⁷ Though undoubtedly a “landmark in the modern control of drugs”⁸, the 1906 Act did not require any premarket approval of new drugs and did not protect consumers against unsafe drugs.⁹ Although the drawbacks of the 1906 Act were readily apparent,¹⁰ increased industry opposition prevented any reform of the food and drug laws for the next thirty-two years.¹¹

B. The Federal Food, Drug, and Cosmetic Act of 1938

As would occur throughout the 20th century, a major public health crisis forced Congress to revisit the scope of federal drug legislation. In September and October of 1937 more than one

1848, 59 Food & Drug. L.J. 169 (2004). For additional background, see Peter Barton Hutt, *Drug Regulations in the United States*, 2 INTL. J. OF TECH. ASSESSMENT IN HEALTH CARE 619, 619 (1986).

⁶ Pure Food and Drugs Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906), *repealed by* Federal Food, Drug, and Cosmetic Act (FDCA), Pub L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21. U.S.C. §§ 301 *et seq.*). The 1906 Act passed with overwhelming support despite heavy opposition from both food and drug manufacturers. For a more detailed discussion of the origins of the 1906 Act see Wallace F. Janssen, *The U.S. Food & Drug Law: How it Came; How it Works*, 35 FOOD DRUG COSM. L.J. 132, 134 (1980).

⁷ Among other things, the 1906 Act prohibited false and misleading labeling of drugs, the distribution of adulterated or misbranded drugs, and required labeling the quantity and ingredients of a small number of particularly dangerous drugs. *See, e.g.*, JAMES HARVEY YOUNG, *PURE FOOD: SECURING THE FEDERAL FOOD AND DRUGS ACT OF 1906* (1989); James L. Zelenay Jr., *The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration Always a Better Food and Drug Administration?*, 60 FOOD & DRUG L.J. 261, 263-264 (2005).

⁸ WILLIAM M. WARDELL & LOUIS LASAGNA, *REGULATION AND DRUG DEVELOPMENT* 6 (1975).

⁹ For additional background about federal food and drug policy in the early 20th century, see PETER TEMIN, *TAKING YOUR MEDICINE: DRUG REGULATION IN THE UNITED STATES* 35-37 (1980).

¹⁰ *See, e.g.*, DEPT. OF AGRIC., 1917 REPORT OF THE USDA BUREAU OF CHEMISTRY, *in* HUTT & MERRILL, *FOOD AND DRUG LAW: CASES AND MATERIALS* 11 (2d ed. 1991).

¹¹ *See* Janssen, *supra* note 6, at 135-37 (discussing defeat of proposed food and drug reforms in 1933 in the wake of massive opposition by the drug and advertising industries).

hundred people died after ingesting Elixir Sulfanilamide.¹² Sulfanilamide had been safely used in caplet form to treat streptococcal infections, but in 1937 the S.E. Massengill Co., responding to consumer demand, developed a liquid version of the drug.¹³ Massengill's scientists found that a solution of diethylene glycol effectively dissolved sulfanilamide and the new elixir successfully passed all tests for flavor, appearance, and fragrance.¹⁴ Massengill, under no obligation to test new drugs for toxicity under the 1906 Act, promptly shipped the new formulation across the country.¹⁵ Had Massengill conducted any tests for safety, the company would have discovered that diethylene glycol, the equivalent of modern day antifreeze, was a deadly poison.¹⁶ Those who died from the drug, many of them children, suffered "intense and unrelenting pain,"¹⁷ and the resultant public outrage prompted Congressional action.

In 1938, Congress enacted the Federal Food, Drug, and Cosmetic Act¹⁸ ("FD&C Act"). The FD&C Act for the first time required drug manufacturers to test all new drugs for safety and obtain FDA approval prior to any commercial distribution.¹⁹ Specifically, the FD&C Act required manufacturers of any "new drug"²⁰ to file a new drug application (NDA) with FDA²¹

¹² See, e.g., Michael D. Greenberg, *AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process*, 3 N.Y.U. J. LEGIS. & PUB. POLY 295, 302 (2000). For a detailed description of the sulfanilamide tragedy and the federal response, see Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER MAGAZINE (Jun. 1981) available at <http://www.fda.gov/oc/history/elixir.html>.

¹³ See Ballentine, *supra* note 12. See also TEMIN, *supra* note 9 at 43.

¹⁴ Ballentine, *supra* note 12.

¹⁵ *Id.*

¹⁶ *Id.* See also REPORT OF THE SEC'Y OF AGRIC. ON DEATHS DUE TO ELIXIR SULFANILAMIDE, S. DOC. NO. 75-124, at 1-3 (2d Sess. 1937).

¹⁷ Ballentine, *supra* note 12.

¹⁸ Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301 *et seq.* [hereinafter "FD&C Act"]).

¹⁹ FD&C Act § 505 (current version at 21 U.S.C. § 355 (2000)).

²⁰ The FD&C Act defined a "new drug" as "(1) Any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use...; or (2) Any drug the composition of

detailing medical and scientific data about the drug's safety for human consumption.²² Though the FD&C Act required an "effective" NDA prior to commercialization of a drug, the 1938 statute provided that a new drug application would automatically become effective after sixty days unless FDA provided affirmative notice to the contrary.²³ Though a sizable increase in regulatory authority from the 1906 Act, the FD&C Act did not therefore constitute true pre-market approval in the sense that we understand it today.

In order to authorize clinical trials intended to determine drug safety, Congress specifically authorized FDA to promulgate regulations exempting "drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety of drugs."²⁴ The FD&C Act did not specifically authorize any investigational use of drugs for treatment. The new act dramatically increased FDA's authority to set safety standards and restrict the availability of dangerous drugs and represented a "major shift toward consumer protection through risk regulation[.]"²⁵

C. The Drug Amendments of 1962

The modern statutory framework under which new drugs are approved today arose out of a second public health crisis in the 1960s. Thalidomide, a drug that had been successfully marketed in Europe during the 1950s to reduce morning sickness in pregnant women, was found

which is such that such drug, as a result of investigations to determine its safety for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions." FD&C Act, Ch. 675, § 201(p), 52 Stat. 1040, 1042 (1938).

²¹ *Id.* at § 505(a).

²² *Id.* at § 505(b).

²³ *Id.* at § 505(c).

²⁴ *Id.* at § 505(i).

²⁵ Greenberg, *supra* note 12, at 302-03.

to have caused severe birth defects in thousands of children.²⁶ Though never approved in the United States, the tragedy brought new public clamor for tougher premarket drug regulation.²⁷ Even though FDA had consistently withheld approval of NDAs for Thalidomide within the sixty-day statutory period required under the 1938 FD&C Act, all that had stood between the public and the dangers of Thalidomide was a single FDA scientist, Dr. Francis Kelsey, who diligently marked each submitted NDA as “incomplete” before each sixty-day statutory deadline.²⁸ Even so, Dr. Kelsey had not withheld approval of Thalidomide based on any indicia of danger in the NDAs themselves (as no such data were present) but rather due to “insufficient information.”²⁹ Because FDA had no authority to supervise clinical testing of new drugs, millions of tablets of thalidomide had been distributed to U.S. physicians in preparation for human testing.³⁰

In direct response to the “near miss”³¹ of a widespread thalidomide disaster, Congress passed the Drug Amendments of 1962³² (Amendments), altering the regulatory landscape in a number of important ways. The Amendments expanded FDA’s mandate with regard to new drug approvals, requiring FDA to determine a new drug’s effectiveness in addition to its safety and

²⁶ See, e.g., HARVEY TEFF & COLIN R. MUNRO, *THALIDOMIDE: THE LEGAL AFTERMATH* 1-10 (1976). For a detailed history of the thalidomide crisis, see THE INSIGHT TEAM OF THE SUNDAY TIMES OF LONDON, *SUFFER THE CHILDREN: THE STORY OF THALIDOMIDE* (1979).

²⁷ See Zelenay, *supra* note 7, at 265.

²⁸ Linda Bren, *Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History*, FDA CONSUMER MAGAZINE (Mar.-Apr. 2001) available at http://www.fda.gov/fdac/features/2001/201_kelsey.html. See also TEMIN, *supra* note 9, at 123.

²⁹ TEMIN, *supra* note 9, at 123.

³⁰ *Id.* at 124.

³¹ See 108 CONG. REC. 21,070 (1962) (statement of Rep. Reuss) (arguing that the thalidomide tragedy demonstrated need for increased FDA authority to prevent a similar incident). See also Zelenay, *supra* note 7, at 266.

³² Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified as amended in scattered sections of 21 U.S.C. §§ 301-381). For a detailed description of the origins and effects of the Drug Amendments of 1962, see Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 GEO. L.J. 185 (1972).

obligating drug sponsors to collect data through “adequate and well controlled investigations, including clinical investigations” conducted by experts.³³ The Amendments instituted the first true requirement of affirmative FDA pre-market approval for new drugs, eliminating the old regime where an NDA could become effective automatically after sixty days.³⁴

The new law required drug sponsors to gain FDA approval prior to undertaking any clinical trials,³⁵ expanding FDA authority to regulate the development of new drugs before a sponsor sought marketing approval.³⁶ The Amendments did not include any statutory provision for investigational use of unapproved drugs for treatment, and limited the IND exemption only for use in clinical investigations.³⁷

D. The New Drug Approval Process

In response to the 1962 Amendments, FDA promulgated complex and detailed regulations establishing pre-market approval procedures for new drugs, requiring extensive testing for both safety and effectiveness under controlled clinical trials.³⁸ These regulations continue to provide the general regulatory framework under which new drugs are developed and approved today.

1. Investigational New Drug (IND) Applications

³³ Drug Amendments of 1962, § 102(c), *amending* Federal Food, Drug & Cosmetic Act of 1938, § 505(d).

³⁴ *Id.* at § 104(b), *amending* Federal Food, Drug, & Cosmetic Act of 1938, § 505(c).

³⁵ *Id.* at § 102(b), *amending* Federal Food, Drug, & Cosmetic Act of 1938, § 505(i).

³⁶ See David W. Jordan, *International Regulatory Harmonization: A New Era in Prescription Drug Approval*, 25 VAND J. TRANSNAT'L L. 471, 478 (1992).

³⁷ Drug Amendments of 1962 at § 102(b).

³⁸ See 21 C.F.R. §§ 312.20 – 312.130 (2007).

FDA's jurisdiction over new drug development begins quite early in the developmental process. In order to conduct any research on human beings, a drug sponsor must first submit an investigational new drug (IND) application."³⁹ However, in order to submit an IND, the drug sponsor must first conduct preclinical investigations on laboratory animals⁴⁰ in order to "identify the nature of the chemical entity being investigated" and to "establish sufficient evidence" of toxicity "to determine if it is reasonably safe for human beings in preliminary clinical investigations."⁴¹ A drug sponsor may need as much as three and a half years to complete pre-clinical investigations and assemble all the necessary data to submit the IND.⁴²

Provided FDA approves the IND application, the drug sponsor may then move on to the first of three phases of required human clinical investigations.⁴³ During Phase I trials, the drug is administered in low doses to a small group of healthy human volunteers, through which researchers obtain toxicity and pharmacology information regarding potential adverse effects on human beings.⁴⁴ These tests are primarily aimed to determine the drug's safety and presumably

³⁹ See 21 C.F.R. §§ 312.20 – 312.38 (2007).

⁴⁰ See 21 C.F.R. § 312.23(a)(8) (2007) (mandating disclosure of pharmacological and toxicological effects on laboratory animals).

⁴¹ See 21 C.F.R. § 312.22 (2007). The IND application must additionally include general information about the drug sponsor and any planned clinical investigations, protocols for the planned studies, detailed information about the drug's chemical nature and any human experience with the drug, and any other relevant information about the drug. See 21 C.F.R. § 312.23.

⁴² See Zelenay, *supra* note 7, at 267.

⁴³ See 21 C.F.R. § 312.21 (2007). After submitting the IND application, a drug sponsor must wait thirty days to allow FDA to review the application. 21 C.F.R. § 312.40(b)(1) (2007). If FDA responds favorably, or does not respond within the thirty-day time period, the sponsor may begin clinical investigations pursuant to the standards set forth in the IND application and in agency regulations. See 21 C.F.R. §§ 312.40(b), 312.50 (2007).

⁴⁴ 21 C.F.R. § 312.21.

will uncover any obvious and substantial negative effects.⁴⁵ Phase I testing requires an average of six to twelve months to complete.⁴⁶

Assuming positive results in Phase I, researchers may then proceed to Phase II. These trials are primarily geared towards determining the drug's effectiveness.⁴⁷ Clinicians conduct controlled studies on a small group of human volunteers, generally involving patients who suffer from the disease or condition that the sponsor intends the drug to treat.⁴⁸ During Phase II, researchers clarify dosage requirements, evaluate the drug's actual therapeutic effects, and compare the new drug's effects with those of currently existing drugs.⁴⁹ Phase II typically lasts between eighteen months and two years.⁵⁰

Phase III represents the longest and most intensive phase of clinical investigations. In order to proceed to Phase III, data from the first two phases must offer a reasonable assurance that the drug is effective and safe, and that the potential benefits of the drug outweigh the risks of a large-scale clinical trial.⁵¹ During this phase, hundreds or thousands of subjects are enrolled to participate in large-scale, generally controlled, clinical trials.⁵² Phase III trials further develop effectiveness data for the investigational drug, closely examine the dose-response relationship of

⁴⁵ See Greenberg, *supra* note 12, at 304.

⁴⁶ See, e.g., Alison R. McCabe, Note, *A Precarious Balancing Act: The Role of FDA as Protector of Public Health and Industry Wealth*, 36 SUFFOLK U. L. REV. 787, 790 n.26 (2003) (citing average of twelve months for Phase I testing). Cf. Charles J. Walsh & Alyssa Pyrich, *Rationalizing the Regulation of Prescription Drugs and Medical Devices; Perspectives on Private Certification and Tort Reform*, 48 RUTGERS L. REV. 883, 906 (1995) (stating typical Phase I tests of approximately six months).

⁴⁷ 21 C.F.R. §312.21(b)

⁴⁸ *Id.*

⁴⁹ *Id.*

⁵⁰ See Zelenay, *supra* note 7 at 267 (stating average Phase II testing lasts for two years). See also Walsh & Pyrich, *supra* note 46, at 907 (reporting average length of 18 months for Phase II trials).

⁵¹ 21 C.F.R. § 312.21(c).

⁵² *Id.*

the new drug, and allow for more data about any potential adverse effects or drug interactions.⁵³

Phase III trials are extremely costly and very time-consuming, lasting an average of three years.⁵⁴

2. The New Drug Application (NDA)

Upon successful completion of all three phases of clinical trials, the drug sponsor may submit a new drug application (NDA) to FDA.⁵⁵ The NDA, a comprehensive and exhaustively detailed application, must include all of the data generated from preclinical and clinical investigations as well as numerous other requirements.⁵⁶ Under the FD&C Act, FDA must technically approve or reject the NDA within 180 days of its filing.⁵⁷ However, FDA has narrowly interpreted the term “filing,” stating that an NDA will not be considered filed until it is “approvable.”⁵⁸ If FDA determines that the application does not contain sufficient information for approval, it need not begin the review process until the sponsor provides the required information.⁵⁹ Once the NDA is “filed,” FDA will make its own determination regarding the

⁵³ *Id.*

⁵⁴ See Zelenay, *supra* note 7 at 267. See also McCabe, *supra* note 46, at 790, n.26.

⁵⁵ 21 U.S.C. § 355(b)(1)(A) (2000). See also 21 C.F.R. § 314.50 (2007). Some drugs, such as generic copies of existing brand name drugs, are eligible to file an abbreviated new drug application (ANDA), which requires substantially less information, in order to expedite the approval process. 21 U.S.C. § 355(j) (2000); 21 C.F.R. § 314.92(a) (2007).

⁵⁶ See 21 U.S.C. § 355(b); 21 C.F.R. § 314.50. The application must include 1) full reports from the preclinical and clinical trials which have been made to show whether the drug is safe and effective for use; 2) a full list of the drug’s ingredients or components; 3) a full statement of the drug’s composition; 4) a full description of manufacturing, processing, and packaging methods and controls; 5) any samples of the drug or of the articles used as components in the drug as may be required by FDA; and 6) samples of the proposed labeling. The NDA must additionally disclose all investigators who worked on the clinical trials and their reports, as well as the patent number and expiration dates of any patents related to or impacted by the drug under consideration. 21 U.S.C. § 355(b)(1); 21 C.F.R. § 314.53(b) (2007).

⁵⁷ 21 U.S.C. § 355(c)(1).

⁵⁸ 21 C.F.R. § 314.125 (2007)

⁵⁹ See Zelenay, *supra* note 7, at 268.

drug's safety and effectiveness, and, upon weighing the potential risks of the new drug against its benefits, determines whether the drug should be approved for commercialization.⁶⁰

The new drug approval process, as developed after 1962, is therefore both extremely labor and cost intensive for potential drug developers. During the 1970s, development costs soared while the development process dragged on – some estimates suggest that the drug development process, spanning from initial research to market, took an average of eight years to complete and cost more than fifty million dollars per drug.⁶¹ These costs have largely increased over time: in 1990, new drug development in the United States was estimated to average nearly twelve years and 230 million dollars per new drug.⁶² More recent surveys from 2000-2002 suggest the average total cost of an NDA for a new chemical entity has risen to approximately \$1.7 billion, while another study indicates that the total time of development, including nonclinical research as well as IND testing and NDA review, had exceeded 14 years by the late 1990s – despite expedited administrative review under the Prescription Drug User Fee Act.⁶³

⁶⁰ *Id.* at 268-69. Other limitations can arise even after approval of the NDA. FDA can withdraw or suspend approval at any time if new evidence suggests the drug is not safe or effective. *See* 21 U.S.C. § 355(e). FDA therefore requires sponsors to provide periodic reports about any adverse effects associated with the drug. *See* FOOD AND DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERVS., MANAGING THE RISKS FROM MEDICAL PRODUCT USE: CREATING A RISK MANAGEMENT FRAMEWORK 52 (1999), *available at*: <http://www.fda.gov/oc/tfrm/1999report.html>. Additionally, FDA can require the drug manufacturer to conduct “Phase IV” postmarket surveillance studies to obtain additional safety and effectiveness data. *See* 21 C.F.R. § 310.303-310.305 (2007). *See also* Zelenay, *supra* note 7, at 270.

⁶¹ *See Revitalizing New Product Development From Clinical Trials Through FDA Review: Hearing on S. 1477 Before the Senate Comm. on Labor and Human Resources*, 104th Cong. 219-30 (1996) (statement of Fred W. Lyons Jr., Chairman, Hoechst Marion Roussel, Inc.). For a summary of the various barriers to drug development, see Greenberg, *supra* note 12.

⁶² *See Drugs and Biologics: Hearings Before the Subcomm. on Oversight and Investigations of the House Comm. on Commerce*, 104th Cong. 1-2 (1995) (statement of Congressman Joe Barton).

⁶³ *See* HUTT, MERRILL & GROSSMAN, FOOD AND DRUG LAW: CASES AND MATERIALS 776-778 (3d ed. 2007). For further statistical information on the rising cost and delay of drug development, *see generally* Tufts Center for the Study of Drug Development, *Longer Clinical Times are Extending Time to Market for New Drugs in U.S.*, 7 IMPACT REP., No. 6 (Nov./Dec.

E. AIDS and The New Pressures of the Consumer Activist Movement

The traditional paradigm of drug regulation, carefully crafted to protect the public from dangerous and ineffective drugs through rigorous pre-approval standards, met new opposition from activists seeking increased access to drugs during the AIDS epidemic of the 1980s.⁶⁴ Acquired Immune Deficiency Syndrome (AIDS), a retroviral disease that hijacks the body's immune system and destroys its ability to combat illness,⁶⁵ first emerged in the early 1980s as disproportionate numbers of homosexual men fell ill to an unknown and deadly illness.⁶⁶ By 1982, the Centers for Disease Control (CDC) had identified the new virus,⁶⁷ but subsequent progress in understanding and treatment of the disease remained quite slow.⁶⁸ In the early years of AIDS, the disease affected primarily politically unpopular minorities such as homosexuals and intravenous drug users, as a result of which mainstream society largely failed to respond.⁶⁹ Despite the looming presence of a serious public health crisis, through 1987 AIDS had not become a major political issue, government research expenditures remained relatively small, and FDA had not approved a single treatment for the disease.⁷⁰ Meanwhile, desperately ill and dying victims of the disease, lacking any legitimate treatment and facing imminent death, fervently

2005); Joseph A. DiMasi, *New Drug Development in the United States 1963 to 1999*, 69 CLINICAL PHARMACOLOGY & THERAPEUTICS 286 (2001).

⁶⁴ For a comprehensive discussion of the ways in which the rise of AIDS challenged the traditional paradigm of FDA's drug approval scheme, see Greenberg, *supra* note 12.

⁶⁵ See PETER S. ARNO & KARYN L. FEIDEN, *AGAINST THE ODDS: THE STORY OF AIDS DRUG DEVELOPMENT, POLITICS, AND PROFITS* 15-17 (1992).

⁶⁶ *Id.* at 2-4.

⁶⁷ *Id.* at 4.

⁶⁸ Greenberg, *supra* note 12, at 309.

⁶⁹ *Id.* at 310. See also ARNO & FEIDEN, *supra* note 65, at 4-5.

⁷⁰ Greenberg, *supra* note 12, at 310.

pursued any available glimmer of hope – no matter how far-fetched or unlikely.⁷¹ Rumors and anecdotes spread about various untested compounds, and persons with AIDS experimented with myriad unknown, generally ineffective, and sometimes dangerous self-treatments.⁷²

The AIDS activist movement arose from this context, as those communities most affected by the virus shared a growing perception that the government response to the AIDS crisis was entirely inadequate.⁷³ Various activist organizations developed to improve the lives of people living with AIDS. Examples include the Gay Men’s Health Crisis, the People With AIDS Health Group, and the AIDS Coalition to Unleash Power (ACT UP), a militant group that utilized confrontational tactics to achieve political and regulatory reform.⁷⁴ Although this grassroots movement pressed for a variety of social and political goals, increased access to experimental and investigational therapies became a key concern. AIDS activism created additional public awareness and increased political pressure on the FDA to promote access to new treatments, and played a key role in efforts to reform FDA’s drug approval process.⁷⁵

A complete description of the reforms achieved during the AIDS crisis is beyond the scope of this paper, but a few noteworthy developments must be acknowledged. Recognizing that patients confronting imminent death face far more limited risks from experimental medication than the general public, and that even the most remote probabilities for improvement may generate enormous benefits, FDA undertook a variety of initiatives to increase access for

⁷¹ *Id.* at 311.

⁷² *Id.* at 311 (describing treatment with remedies such as AL-721, derived from egg yolks, attempts by persons with AIDS to synthesize remedies using “kitchen chemistry,” and the rise of black market buying clubs to facilitate purchase of drugs available overseas. *See also* ARNO & FEIDEN, *supra* note 65, at 60-70.

⁷³ *See* Greenberg, *supra* note 12, at 310-12.

⁷⁴ *Id.* at 311-12. *See also* ARNO & FEIDEN, *supra* note 65, at 65-68, 73-82.

⁷⁵ *See* Greenberg, *supra* note 12, at 312.

unapproved treatments and expedite approval processes for new drugs for untreatable illnesses.⁷⁶ Between 1987 and 1993, FDA formalized various exemptions to the IND application process allowing for treatment and emergency use of investigational drugs for seriously ill patients,⁷⁷ promulgated “Subpart E”⁷⁸ and “accelerated approval”⁷⁹ regulations designed to expedite FDA review of new drugs designed to treat life-threatening or seriously debilitating diseases⁸⁰, and instituted the “parallel track” program for expanded access specifically to HIV/AIDS therapies.⁸¹

F. The Food and Drug Administration Modernization Act of 1997

The efforts to expand access for the seriously ill in the wake of AIDS reflect a tension at the heart of FDA’s regulatory mandate: while the traditional regulatory mission to protect the public from dangerous or ineffective drugs generally serves the public good, that mission can impose increased harm to those whose interests are primarily threatened by an absence of

⁷⁶ *Id.* at 315.

⁷⁷ See *infra* Section III, notes 134 to 158 and accompanying text.

⁷⁸ See 21 C.F.R. § 312.80 (2007).

⁷⁹ See 21 C.F.R. § 314.500 (2007) (providing for accelerated approval of drugs); 21 C.F.R. § 601.4 (2007) (providing for accelerated approval of biologicals, such as vaccines.)

⁸⁰ Subpart E established a variety of measures to expedite review of new drugs for serious diseases such as AIDS, including early and repeated FDA consultation with pharmaceutical developers to speed the clinical trial process, consolidation of Phase II and III clinical testing, and use of increased “Phase IV” post-marketing trials to postpone the burden of additional safety research until after approval. See 21 C.F.R. § 312.82 (2007) (early consultation between FDA and drug sponsors); 21 C.F.R. § 312.87 (2007) (FDA involvement in clinical trials); 21 C.F.R. § 312.85 (2007) (Phase IV post-marketing trials). Accelerated approvals regulations went even further, allowing for the use of “surrogate endpoints” in clinical trials, allowing FDA to approve a drug based on measurements other than increased patient survival, such as measuring CD4 cell counts in AIDS patients. See 21 C.F.R. § 314.510 (2007).

⁸¹ See Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People With AIDS and other HIV-Related Disease, 57 Fed. Reg. 13,250 (1992). The parallel track policy, while similar to the Treatment IND regulations, derived from an earlier expanded access collaboration with the National Cancer Institute, described *infra*, Section III notes 173 to 182 and accompanying text. For a more detailed description of the parallel track policy, see *infra* Section III, notes 163 to 172 and accompanying text.

treatment.⁸² The reform measures of the late 1980s and 1990s addressed this tension, but by no means resolved it. Those who face life-threatening diseases for which no viable treatment options exist, continue to argue that the pace of drug development remains too slow and access either too restrictive, too confusing, or both.

While the use of investigational drugs for therapy, rather than for investigation, is actually quite common, the regulatory landscape remains unclear. Many types of “expanded access” programs exist under different names and terminologies, but only a handful of such programs are actually reflected in the IND regulations⁸³ -- and even those that are specifically referred to in the regulations are not necessarily defined.⁸⁴ Additionally, the existing IND regulations failed to address various specific criteria governing FDA’s decision to allow access in a variety of situations.⁸⁵

Responding in part to criticisms that FDA’s procedures had led to inconsistent policies, inequitable access, and preferential access for certain categories of disease, Congress undertook a major initiative to revise FDA’s statutory mandate.⁸⁶ In 1997, Congress enacted the Food and Drug Administration Modernization Act (FDAMA),⁸⁷ a broad piece of legislation that amended numerous sections of the FD&C Act. The full effect of FDAMA lies beyond the scope of this paper. However, a key aspect of the statute, inserted as § 561 of the FD&C Act, provides specific statutory authority for expanded access to investigational drugs.⁸⁸

⁸² Greenberg, *supra* note 12, at 328.

⁸³ *See infra*, Section III.

⁸⁴ *See* HUTT, MERRILL & GROSSMAN, *supra* note 63 at 652.

⁸⁵ *See infra*, Section III.

⁸⁶ *See* Proposed Rules to Expand Access, *supra* note 1, at 75149.

⁸⁷ Food and Drug Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997) (codified as amended in scattered sections of 21 U.S.C.) [hereinafter FDAMA].

⁸⁸ FDAMA § 402, 21 U.S.C. § 360bbb (2000) (expanded access to unapproved therapies and diagnostics).

As described in the next section of this paper, FDAMA’s provisions largely parallel existing FDA regulations. Mirroring the emergency use IND regulation⁸⁹, the Act grants discretion to FDA to provide investigational drugs or devices for “the diagnosis, monitoring, or treatment of a serious disease or condition in emergency situations.”⁹⁰ Similarly, § 561(c) parallels FDA’s treatment IND regulations,⁹¹ authorizing the FDA to permit expanded access to an investigational drug or device if 1) it is intended to treat a “serious or immediately life-threatening disease or condition;” 2) no “comparable or satisfactory alternative therapy” is available for the patients to which the drug or device will be administered; 3) the drug or device is currently in a controlled clinical trial under a traditional IND or all clinical trials necessary for approval have been completed; and 4) the drug sponsor is “actively pursuing marketing approval” of the drug or device with “due diligence.”⁹² The statute also requires that any use under a treatment IND must not interfere with “the enrollment of patients in ongoing clinical trials,”⁹³ that for treatment of a “serious disease” there must be “sufficient evidence of safety and effectiveness” to support use of the drug for treatment,⁹⁴ and that for treatment of a “life-threatening disease” the “available scientific evidence, taken as a whole” must provide a “reasonable basis to conclude” that the drug or device “*may* be effective for its intended use and would not expose patients to an unreasonable and significant risk of illness or injury.”⁹⁵

⁸⁹ 21 C.F.R. § 312.36 (2007).

⁹⁰ 21 U.S.C. § 360bbb(a).

⁹¹ 21 C.F.R. § 312.34 (2007).

⁹² 21 U.S.C. § 360bbb(c)(1)-(4).

⁹³ *Id.* at § 360bbb(c)(5).

⁹⁴ *Id.* at § 360bbb(c)(6).

⁹⁵ *Id.* at § 360bbb(c)(7) (emphasis added).

§ 561(b) allows for individual patient access to investigational products for serious diseases.⁹⁶ Although this provision does not mirror any existing FDA regulations, it simply codifies longstanding agency practice.⁹⁷ The act provides that any patient, acting through a physician, may request and obtain access to an investigational drug or device for treatment of a “serious disease or condition” directly from a “manufacturer or distributor” if 1) the licensed physician determines that the patient has no satisfactory alternative therapy to treat the disease or condition, 2) FDA determines there is “sufficient safety and effectiveness to support the use” of the drug or device, 3) FDA determines that providing the drug or device will not interfere with “the initiation, conduct, or completion of clinical investigations to support marketing approval” and 4) the sponsor of the drug or device has submitted a clinical protocol under § 505(i) of the FD&C Act.⁹⁸

The three types of expanded access programs included in FDAMA’s amendments to the FD&C Act did not, therefore, expand access beyond already existing agency practice. Further, FDAMA did little to clarify the confusing landscape of FDA regulations, guidance, and policy in this area. In the wake of the new legislation, patient advocacy groups and other organizations have increasingly pressured FDA to modify existing regulations and clarify agency policy.⁹⁹ In order to “further address the concerns that motivated Congress” to include expanded access provisions in FDAMA¹⁰⁰, FDA has proposed new rules detailing requirements for expanded access to investigational drugs¹⁰¹ and charging for investigational drugs.¹⁰²

⁹⁶ *Id.* at § 21 U.S.C. §360bbb(b).

⁹⁷ See Proposed Rules to Expand Access, *supra* note 1, at 75148. See also HUTT, MERRILL & GROSSMAN, *supra* note 63, at 653.

⁹⁸ 21 U.S.C. § 360bbb(b).

⁹⁹ See *infra*, Section IV.

¹⁰⁰ Proposed Rules to Expand Access, *supra* note 1, at 75149.

¹⁰¹ *Id.*

The next section of this paper discusses the various methods through which FDA permits expanded access to investigational drugs under the current statutory and regulatory scheme, and under informal agency policy.

III. USE OF INVESTIGATIONAL DRUGS FOR TREATMENT

A. Administrative History of “Expanded Access”

As described previously, Section 505(i) of the FD&C Act was originally included in the 1938 statute, and amended in 1962, specifically to authorize clinical investigations used to gather data necessary for submission of an NDA.¹⁰³ So too, at least until the Drug Amendments of 1962, the agency’s regulations specifically required that investigational drugs be made available “solely for investigational use by or under the direction of an expert qualified by scientific training and experience to investigate the safety of such drug.”¹⁰⁴ Prior to 1962, no FDA publications or articles discussing the new drug approval process specifically addressed the use of investigational drugs for therapy outside of clinical investigations.¹⁰⁵

Simultaneously, since 1938 FDA has consistently maintained the position that a drug cannot be “commercialized” prior to approval.¹⁰⁶ IND regulations promulgated in 1962 specified that a drug sponsor can neither “commercially distribute nor test-market” a drug before approval and that FDA can terminate an IND upon learning that the drug “is being or is to be sold or otherwise distributed for commercial purposes not justified by the requirements of the

¹⁰² Proposed Rules for Charging, *supra* note 2.

¹⁰³ See *supra*, notes 24 & 35 and accompanying text.

¹⁰⁴ 21 C.F.R. § 130.2(a)(2)(1962). See also HUTT, MERRILL & GROSSMAN, *supra* note 63, at 651.

¹⁰⁵ HUTT, MERRILL & GROSSMAN, *supra* note 63, at 651.

¹⁰⁶ *Id.*

investigation.”¹⁰⁷ Beginning in 1963, this ban on pre-approval “commercialization” of an investigational drug, absent very unusual circumstances, was additionally reflected on the IND form itself, which required sponsors who intended to charge for an investigational drug to provide “a full explanation why sale is required and should not be regarded as the commercialization of a new drug for which an application is not approved.”¹⁰⁸

In fact, however, FDA has a long history of permitting the use of investigational drugs for treatment outside of clinical trials, dating as far back as 1962.¹⁰⁹ For instance, orphan drugs have been used for treatment use under INDS since 1962.¹¹⁰ Additionally, several thousand patients in the 1970s received the drug metoprolol, a cardioselective β -blocker, under a “treatment protocol” outside the clinical trial process.¹¹¹ Similarly, in the 1980s various antiarrhythmic drugs were made available to over 20,000 patients with complex, life-threatening arrhythmia prior to any NDA approval.¹¹² Beginning in the mid-1970s, FDA and the National Cancer Institute (NCI) organized a system to distribute promising “Group C cancer drugs” to

¹⁰⁷ 27 Fed. Reg. 7990 (Aug. 10, 1962), 28 Fed. Reg. 179 (Jan. 8, 1963), codified at 21 C.F.R. 130.3(a)(11), 130.3(d)(8) (1962) *See also* HUTT, MERRILL & GROSSMAN, *supra* note 63, at 651.

¹⁰⁸ HUTT, MERRILL & GROSSMAN, *supra* note 63, at 651.

¹⁰⁹ *See, e.g.*, Proposed Rules for Expanded Access, *supra* note 1, at 75148; *see also* FDA, “Speeding Access to Important Therapeutic Agents,” <http://www.fda.gov/oashi/speedaccess.html> (last accessed Mar. 30, 2008); HUTT, MERRILL & GROSSMAN, *supra* note 84 at 651; Myron L. Marlin, *Treatment INDs: A Faster Route to Drug Approval?*, 39 AM. U. L. REV. 171, 187 (1989); Frank E. Young, John A. Norris, Joseph A. Levitt & Stuart L. Nightingale, *The FDA’s New Procedures for the Use of Investigational Drugs in Treatment*, 259 JAMA 2267 (Apr. 15, 1988) (describing instances of access to investigational drugs dating back to 1976).

¹¹⁰ *See infra* notes 195 to 203 and accompanying text.

¹¹¹ *See* Young, *supra* note 109, at 2267.

¹¹² *Id.*

patients in need.¹¹³ These “treatment protocols” all arose after basic studies of a drug were “well under way” and “early clinical evidence appeared strongly favorable.”¹¹⁴

In response to the AIDS epidemic of the 1980s, FDA formally promulgated regulations codifying treatment use procedures. The proposed IND rules issued in 1983 intended to expressly authorize the use of a treatment IND or protocol and sought to clarify the circumstances under which patients could obtain access, the universe of eligible drugs, and the procedures by which such drugs could be obtained.¹¹⁵ Though narrowly targeted to combat AIDS, the treatment use regulations codified the same principles FDA had relied upon informally under the Group C protocol with NCI.¹¹⁶ Broader “compassionate use” and “open label” protocols have never been included in formal agency regulations.

The 1983 proposals also contained a provision allowing for “emergency procedures” where a need for an investigational drug might arise in an “emergency situation that does not allow time for compliance with applicable IND submission requirements.”¹¹⁷ The proposed rules permitted FDA to authorize shipment of an investigational drug before submission of an IND, in accord with then existing informal agency practice.¹¹⁸

¹¹³ *Id.* See also FOOD AND DRUG ADMIN., REPORT TO CONGRESS: PATIENT ACCESS TO NEW THERAPEUTIC AGENTS FOR PEDIATRIC CANCER (Dec. 2003), *available at*: <http://www.fda.gov/oashi/speedaccess.html> (follow “Expanded Access” hyperlink) (last visited Mar. 30, 2008); Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations, 48 Fed. Reg. 26720, 26728 (Jun. 9, 1983) (describing informal access to investigational drugs under a physician- or commercial-sponsored IND or protocol where literature reflects that a new drug “shows promise for a serious disease”).

¹¹⁴ Young, *supra* note 109 at 2267.

¹¹⁵ Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations, 48 Fed. Reg. at 26729.

¹¹⁶ *Id.*

¹¹⁷ *Id.* at 26730.

¹¹⁸ *Id.*

FDA makes investigational drugs available to desperately ill patients outside of clinical investigations under a wide range of programs. Although the public often refers to these programs as “compassionate use,” that particular terminology never occurs in FDA regulations.¹¹⁹ Rather, a variety of programs exist all of which might fairly be termed “expanded access” but none of which are specifically referred to as such. The majority of available programs are never mentioned in the IND regulations – and even those that are mentioned are sometimes largely undefined.¹²⁰ The next section of this paper outlines the various methods under which FDA currently allows access to investigational drugs.

B. Currently Available Methods of Access to Investigational Drugs for Treatment

1. Individual Patient IND

FDA has long granted “single patient exceptions” for treatment use of an investigational drug.¹²¹ Unlike treatment protocols, in which a drug is made available to a group of patients suffering from a serious or life-threatening illness, single patient exceptions allow treatment use in an individual patient,¹²² and may permit an entirely new use of a drug or grant an exception to ongoing clinical trials for a patient who failed to meet protocol eligibility requirements.¹²³ Single patient exceptions can be obtained as an amendment to an existing IND or as an entirely

¹¹⁹ See FOOD AND DRUG ADMIN., REPORT TO CONGRESS: PATIENT ACCESS TO NEW THERAPEUTIC AGENTS FOR PEDIATRIC CANCER, *supra* note 113 at 13.

¹²⁰ See HUTT, MERRILL & GROSSMAN, *supra* note 63, at 652.

¹²¹ See, e.g., FOOD AND DRUG ADMIN., BRIEFING DOCUMENT FOR THE ODAC: SINGLE PATIENT USE OF INVESTIGATIONAL CANCER AGENTS (2000); *available at* <http://www.fda.gov/OHRMS/DOCKETS/AC/01/briefing/3757b1.html> (last accessed Mar. 31, 2008) [hereinafter BRIEFING DOCUMENT FOR THE ODAC]. See also HUTT, MERRILL & GROSSMAN, *supra* note 63 at 653 (noting agency use of single patient exceptions since 1962).

¹²² BRIEFING DOCUMENT FOR THE ODAC, *supra* note 121.

¹²³ See FOOD AND DRUG ADMIN., REPORT TO CONGRESS: PATIENT ACCESS TO NEW THERAPEUTIC AGENTS FOR PEDIATRIC CANCER, *supra* note 113 at 13.

new IND.¹²⁴ The individual patient IND can be submitted either by a drug manufacturer, generally as an amendment to an existing IND, or by an individual physician or clinical investigator on behalf of a patient.¹²⁵ Where the manufacturer will not sponsor a patient, a clinical investigator or physician must obtain the drug from a willing manufacturer and then apply directly to FDA for a new IND.¹²⁶ The application must include a brief clinical history of the patient, a proposed treatment plan, a statement of authorization from a willing drug manufacturer or supplier, as well as various other FDA forms.¹²⁷ Additionally, the sponsor must obtain informed consent from the patient as well as approval from the appropriate Institutional Review Board (IRB).¹²⁸ FDA may exercise discretion to disallow further enrollment under individual patient INDs¹²⁹ or, if circumstances occur warranting imposition of a clinical hold under FDA regulations¹³⁰, FDA may terminate or deny treatment under the IND.

The single patient IND does not officially reflected in current FDA regulations. In 1997, Congress included § 561(b) in FDAMA in order to address concerns of inconsistent or arbitrary implementation of access to single patient INDs in the absence of specific guiding criteria from

¹²⁴ *Id.*

¹²⁵ *Id.*

¹²⁶ BRIEFING DOCUMENT FOR THE ODAC, *supra* note 121.

¹²⁷ See FDA, “Physician Request for a Single Patient IND for Compassionate or Emergency Use,” available at <http://www.fda.gov/cder/cancer/singlind.htm> (last accessed Mar. 31, 2008).

¹²⁸ *Id.* See also FOOD AND DRUG ADMIN., REPORT TO CONGRESS: PATIENT ACCESS TO NEW THERAPEUTIC AGENTS FOR PEDIATRIC CANCER, *supra* note 113, at 13.

¹²⁹ See, e.g., *Kuromiya v. United States*, 37 F. Supp. 2d 717, 78 F. Supp. 2d 367 (E.D. Pa. 1999) (upholding decision of Dept. of Health & Human Services to cease enrolling participants in a medical marijuana program established under single patient INDs in 1978, and to gradually phase out the program as participants died or voluntarily left).

¹³⁰ See 21 C.F.R. § 312.42 (2007). In *Smith v. Shalala*, 954 F. Supp. 1 (D.D.C. 1996), the plaintiff, suffering from Hodgkin’s disease, sought a preliminary injunction against FDA preventing the agency from terminating his use of Antineoplasatons, an unapproved drug improperly administered by his physician outside the provisions of an IND. The court denied the injunction, holding that, where a terminally ill patient had failed to make use of available FDA-approved drugs for his condition, the agency could lawfully disallow a single patient exception for an investigational drug, pursuant to 21 C.F.R. § 312.42(b)(1)(i).

FDA.¹³¹ Under the statute, any patient, acting through a licensed physician, may seek access to an investigational drug directly from the manufacturer if 1) the physician determines that no comparable or satisfactory alternative therapy exists to treat the patient's condition and that the probable risk incurred from use of the investigational drug does not outweigh the probable risk from the patient's condition; 2) sufficient evidence of safety and effectiveness exists to support the use of the investigational drug; 3) use of the drug will not interfere with any clinical investigations intended to support marketing approval; and 4) the drug sponsor or clinical investigator submits a clinical protocol consistent with the IND regulations.¹³² The procedures are identical for investigational medical devices.¹³³ The statute is thus consistent with longstanding informal agency practice.

2. Emergency Use IND

As discussed earlier, FDA formally codified emergency use IND procedures in 1987,¹³⁴ but, like single patient exceptions, emergency use procedures date back as far as 1962.¹³⁵ Under the 1987 regulations, FDA may authorize shipment of an investigational drug for a specified use in advance of submission of an IND, where an "emergency situation" does not allow time to properly submit an IND pursuant to §§ 312.23 or 312.34.¹³⁶ "Emergency use" is defined as "the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB

¹³¹ See *supra*, notes 96 to 98 and accompanying text.

¹³² 21 U.S.C. § 360bbb(b).

¹³³ *Id.*

¹³⁴ 52 Fed. Reg. at 8820-8821 (Mar. 19 1987) (codified at 21 C.F.R. § 312.36).

¹³⁵ See HUTT, MERRILL & GROSSMAN, *supra* note 63, at 653.

¹³⁶ 21 U.S.C. § 312.36.

approval.”¹³⁷ Emergency use of a test article may be exempt from prior IRB review, so long as the use of the article is reported to the IRB within 5 business days.¹³⁸ Under the regulations, any subsequent use of the test article must be subject to IRB review,¹³⁹ but FDA also acknowledges that “it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.”¹⁴⁰

Even for an emergency use, an investigator generally must obtain the patient’s informed consent before beginning treatment. Treatment may be provided absent informed consent, however, where both the investigator and a physician not otherwise participating in the investigation certify in writing that 1) the patient is confronted by a life-threatening situation necessitating the use of the test article; 2) informed consent cannot be obtained due to an inability to communicate with, or obtain legally effective consent from, the patient; 3) time is not sufficient to obtain consent from the patient’s legal representative; and 4) no alternative method of approved or generally recognized therapy can provide an equal or greater likelihood of saving the patient’s life.¹⁴¹ If the investigator believes that immediate use of the test article is necessary to preserve the life of the patient, and that sufficient time does not exist to make any written determinations, the investigator must make those determinations within 5 working days of the use of the article, and obtain review from a physician not otherwise involved in the investigation.¹⁴²

¹³⁷ See 21 C.F.R. § 56.102(d).

¹³⁸ See 21 C.F.R. § 56.104(c).

¹³⁹ *Id.*

¹⁴⁰ FDA, GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS AND CLINICAL INVESTIGATORS, 1998 UPDATE, *available at* <http://www.fda.gov/oc/ohrt/irbs/drugsbiologics.html#emergency> (last accessed Mar. 31, 2008).

¹⁴¹ See 21 C.F.R. § 50.23(a).

¹⁴² 21 C.F.R. § 50.23(b).

Congress provided specific statutory authority for emergency use INDs in § 561(a) of the FD&C Act, inserted in 1997 as part of FDAMA.¹⁴³ Under the statute, FDA has discretion “under appropriate conditions” to authorize shipment of investigational drugs or devices for treatment of a “serious disease or condition in emergency situations.”¹⁴⁴ The statute did not, therefore, expand access beyond already existing agency practice.

In the wake of the September 11, 2001 terrorist attacks, Congress enacted the Project BioShield Act of 2004¹⁴⁵ and thereby added § 564 to the FD&C Act,¹⁴⁶ allowing FDA to authorize use of an unapproved new drug during a declared domestic, military, or national security emergency. Since that time, FDA has twice authorized emergency use of the anthrax vaccine by military personnel at the request of the Department of Defense.¹⁴⁷

3. Treatment IND

As discussed above,¹⁴⁸ treatment IND and treatment protocol procedures existed informally for many years before FDA proposed formal regulations detailing agency practice in 1983. The final rules were promulgated in 1987 at the peak of the AIDS crisis and included broader provisions than the original proposal.¹⁴⁹

The treatment IND procedure was intended to “facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible” before the marketing process begins, and also to gather additional data on the drug’s safety and

¹⁴³ 21 U.S.C. § 360bbb(a).

¹⁴⁴ *Id.*

¹⁴⁵ Pub L. No. 108-276, § 4(a), 118 Stat. 835 (2004).

¹⁴⁶ 21 U.S.C. § 360bbb(3).

¹⁴⁷ *See* 70 Fed. Reg. 5450 (Feb. 2, 2005), 70 Fed. Reg. 44657 (Aug. 3, 2005).

¹⁴⁸ *See supra* at notes 115 to 117 and accompanying text.

¹⁴⁹ *See* Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale, 52 Fed. Reg. 19466 (May 22, 1987).

effectiveness.¹⁵⁰ Under FDA regulations, the agency will permit the treatment use of an investigational drug under an IND or treatment protocol if 1) the drug is intended to treat a serious or immediately life-threatening disease; 2) no comparable or satisfactory alternative therapy exists to treat the intended patient population; 3) the drug is under investigation under a controlled clinical trial under an IND, or all clinical trials are complete; and 4) the drug sponsor is actively pursuing market approval with due diligence.¹⁵¹ For treatment of a serious disease, FDA may deny treatment use of an investigational drug absent sufficient evidence of safety and effectiveness.¹⁵² For an immediately life-threatening disease, FDA may deny a request for treatment use of the drug only if the scientific evidence, taken as a whole, does not provide a reasonable basis to conclude that the drug may be effective for its intended use in its intended patient population or that the drug would not expose patients to an unreasonable and significant risk of illness or injury.¹⁵³ The regulations define “immediately life-threatening” as a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without treatment.¹⁵⁴

The final rule further clarified that treatment use of an investigational drug would be conditioned upon the drug sponsor or any investigators complying with all FDA regulations governing informed consent,¹⁵⁵ IRBs,¹⁵⁶ and any other applicable provisions of Part 312.¹⁵⁷

The final regulation also grants authority for drug sponsors to charge for investigational drugs accessed under a treatment IND – a key factor distinguishing treatment INDs from other

¹⁵⁰ 21 C.F.R. § 312.34.

¹⁵¹ *Id.*

¹⁵² 21 C.F.R. § 312.34(b)(2).

¹⁵³ 21 C.F.R. § 312.34(3)(i).

¹⁵⁴ 21 C.F.R. § 312.34(b)(3)(ii).

¹⁵⁵ 21 C.F.R. § 50 (2007).

¹⁵⁶ 21 C.F.R. § 56 (2007).

¹⁵⁷ *See* 21 C.F.R. § 312.34(c).

informal agency policies such as open label protocols. The regulation permits a drug sponsor to charge for access under a treatment IND provided that 1) there is adequate enrollment in any ongoing clinical trials under the authorized IND; 2) charging does not constitute commercial marketing of a new unapproved drug; 3) the drug is not advertised or otherwise commercially promoted; and 4) the sponsor is actively pursuing marketing approval with due diligence.¹⁵⁸

The provisions on charging go beyond treatment INDs and specify other limitations on charging for investigational drugs. FDA has specified that charging for a drug in clinical trials under an IND remains impermissible absent prior written approval from the agency upon a request from the sponsor detailing why distribution of the drug to test patients should not be considered part of the normal cost of doing business.¹⁵⁹ Under the general provision on charging, in all cases where a sponsor is permitted to charge for an investigational drug, FDA does not allow a sponsor to charge “a price larger than that necessary to recover costs of manufacture, research, development, and handling of the investigational drug.”¹⁶⁰

Congress provided specific statutory authority for treatment INDs in § 561(c) of the FD&C Act, inserted in 1997 as part of FDAMA, but notably did not include any provision on charging.¹⁶¹ The statute tracks then existing regulations and did not therefore expand access beyond prior agency practice.¹⁶²

4. Parallel Track IND

¹⁵⁸ See 21 C.F.R. § 312.7(d)(2).

¹⁵⁹ See 21 C.F.R. § 312.7(d)(1).

¹⁶⁰ 21 C.F.R. § 312.7(d)(3).

¹⁶¹ 21 U.S.C. § 360bbb(c).

¹⁶² See *supra*, notes 91 to 95 and accompanying text.

In 1990, as a result of continued pressure from the AIDS community¹⁶³, the Public Health Service and FDA announced a “parallel track mechanism,” an expanded access protocol intended exclusively for AIDS/HIV patients.¹⁶⁴ The parallel track IND, while conceptually similar to the treatment IND codified several years earlier, was intended to speed approval of expanded access protocols “for promising investigational drugs when the evidence for effectiveness is less than that generally required for a treatment IND.”¹⁶⁵ As such, drugs would become available earlier in the development process, perhaps at the close of Phase I clinical trials.¹⁶⁶ Under this policy, promising new drugs would be made available through studies without concurrent control groups to monitor drug safety. These studies would be conducted in “parallel” with clinical trials under a traditional IND.¹⁶⁷

Patients eligible to receive investigational drugs under the parallel track mechanism must 1) have significant HIV-related illness or be at imminent health risk due to HIV-related immunodeficiency; and 2) be unable to participate in controlled clinical trials because the patient either does not meet the trial entry criteria, is too ill to participate, would suffer undue hardship through participation, or the controlled clinical trials are fully enrolled; and 3) the patient cannot take the “standard treatment” because it is “contraindicated, cannot be tolerated, or is no longer

¹⁶³ See, e.g., “FDA Responds to Act Up Demands,” FDA Talk Paper No. T88-74 (Oct. 5, 1988); see also Dick Thompson, *Drugs from the Underground*, TIME MAG., July 10, 1989, at 49.

¹⁶⁴ See Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People With AIDS and Other HIV-Related Diseases, 55 Fed. Reg. 20856 (May 21, 1990).

¹⁶⁵ See Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People With AIDS and other HIV-Related Diseases, 57 Fed. Reg. 13,250, 13,256 (Apr. 15, 1992).

¹⁶⁶ See Sheila R. Shulman & Jeffrey S. Brown, *The Food and Drug Administration’s Early Access and Fast-Track Approval Initiatives: How Have They Worked?*, 50 FOOD & DRUG L.J. 503, 509 (1995).

¹⁶⁷ Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People With AIDS and other HIV-Related Diseases, 57 Fed. Reg. at 13256.

effective.”¹⁶⁸ Physicians participating in parallel track studies must generally comply with all IND requirements. The parallel track studies provide additional data on safety and effectiveness, and include monitoring and reporting requirements running concurrent with controlled clinical trials.¹⁶⁹

In order to balance the heightened risk to patients incurred through earlier access to parallel track drugs, the policy imposes additional layers of oversight through a multi-agency review process.¹⁷⁰ Both the AIDS Research Advisory Council (ARAC) and the National Institutes of Health (NIH) advise the FDA and assist the agency in selecting promising new therapies. Further, the policy calls for the creation of a National Human Subjects Protection Review Panel to ensure that all protocols comply with legal and ethical requirements.¹⁷¹

Despite intentions to speed access to investigational drugs to large patient populations early in the development process, the policy does not provide any unique authorization permitting manufacturers or sponsors to charge for access to the drugs. Any sponsor seeking to charge for access must therefore comply with 21 C.F.R. § 312.7(d)(1), obtaining written authorization to charge from FDA after a full explanation detailing why access to the drugs should not be considered part of the normal costs of business.¹⁷²

The parallel track policy is not codified in the Code of Federal Regulations and can only be found in the Federal Register.

5. Group C Cancer Treatment IND

¹⁶⁸ *Id.* at 13257.

¹⁶⁹ *Id.* at 13258.

¹⁷⁰ *Id.* at 13257.

¹⁷¹ *Id.* See also Shulman & Brown, *supra* note 166 at 509.

¹⁷² Shulman & Brown, *supra* note 166, at 517.

The Division of Cancer Treatment at NCI plays a major role in the development of new anticancer drugs.¹⁷³ Since the 1970s, FDA and NCI have collaborated to provide early access to promising investigational anticancer drugs to patients in need.¹⁷⁴ Treatment under NCI's Group C designation resembles the treatment IND in that it allows broadened access to promising investigational drugs that demonstrate reproducible activity fighting tumors.¹⁷⁵ Under NCI's distribution system, Group C drugs are distributed to qualified physicians who have registered to provide the drug to patients under a protocol outside traditional clinical trials.¹⁷⁶ Drugs designated under the Group C classification appear in a Master File submitted to FDA.¹⁷⁷ The Cancer Treatment Evaluation Program (CTEP) may then submit a formal application to FDA to authorize Group C distribution by NCI for the particular indications described in the application.¹⁷⁸ Inclusion in a Group C protocol does not constitute a marketing application and does not replace FDA's formal conclusion about a drug's safety and effectiveness, however, drugs are generally only included in a Group C protocol when approval of an NDA is "considered likely in the relatively near future."¹⁷⁹ Inclusion in a Group C protocol generally

¹⁷³ See Anticancer Drug Development: Memorandum of Understanding with the National Institutes of Health, 44 Fed. Reg. 25510 (May 1, 1979).

¹⁷⁴ See, e.g., Young, *supra* note 109, at 2268.

¹⁷⁵ See FOOD AND DRUG ADMIN., REPORT TO CONGRESS ON PATIENT ACCESS TO NEW THERAPEUTIC AGENTS FOR PEDIATRIC CANCER, *supra* note 113 at 16.

¹⁷⁶ See NCI, Understanding the Approval Process for New Cancer Treatments (Jan 6, 2004), available at: <http://www.cancer.gov/clinicaltrials/learning/approval-process-for-cancer-drugs/page4> (last accessed Apr. 1, 2008).

¹⁷⁷ See Anticancer Drug Development: Memorandum of Understanding with the National Institutes of Health, 44 Fed. Reg. at 25510; see also HUTT, MERRILL & GROSSMAN, *supra* note 63, at 655.

¹⁷⁸ See FOOD AND DRUG ADMIN., REPORT TO CONGRESS ON PATIENT ACCESS TO NEW THERAPEUTIC AGENTS FOR PEDIATRIC CANCER, *supra* note 105, at 16.

¹⁷⁹ *Id.*

entails various safety reporting requirements, and each protocol specifies particular patient eligibility, drug use, and reporting mechanisms.¹⁸⁰

The Group C program is not codified in any regulations. However, the program was incorporated in a Memorandum of Understanding between FDA and NCI published in the Federal Register.¹⁸¹ Although NCI continues to designate these drugs as “Group C,” since 1988 FDA has referred to this protocol as “treatment IND/Group C” and treats applications under the protocol as “treatment IND requests, no matter what name they come under,” relying on the same criteria used in ordinary treatment IND requests. NCI pays for the drugs and patients are not charged to receive treatment under a Group C IND.¹⁸²

6. Open Label IND

An open label IND or open label protocol is another pathway to access outside of controlled clinical trials. Two types of open protocols exist. First, an open label protocol may be used under a wide variety of circumstances to treat seriously ill patients. The protocol allows patients to receive the drug while some safety information is collected, but the study has no control group.¹⁸³ This mechanism is similar to a single patient IND, but allows FDA to process requests for multiple individuals through a single general request from the drug sponsor.¹⁸⁴ Similar to other FDA policies, open label protocols may be appropriate where a licensed physician has determined that an unapproved drug may benefit a particular patient, no other

¹⁸⁰ See NCI, Understanding the Approval Process of New Cancer Treatments, *supra* note 176.

¹⁸¹ See Anticancer Drug Development: Memorandum of Understanding with the National Institutes of Health, 44 Fed. Reg. at 25510.

¹⁸² See HUTT, MERRILL & GROSSMAN, *supra* note 63, at 656.

¹⁸³ See *Clinical Trial Subjects: Adequate FDA Protections?: Hearing Before the H. Comm. on Govt. Reform & Oversight*, 105th Cong. 60-61 (1998) (Statement of Dr. Michael A. Friedman, M.D., Lead Deputy Comm’r. of FDA).

¹⁸⁴ *Id.*

alternative therapies are available, and sufficient evidence of safety and effectiveness exists to support use of the investigational product.¹⁸⁵ Unlike the treatment IND, the sponsor must agree to provide the drug free of charge, absent specific approval from FDA to charge under 21 C.F.R. § 312.7(d)(1).

The other type of open label protocol arises when a placebo-controlled clinical trial has been completed. Sometimes referred to as an “open label extension,” this mechanism allows continued treatment after a clinical trial, and permits patients who had received a placebo under the trial to receive the unapproved drug.¹⁸⁶

Open label INDs date back to 1962 but have never been codified in any FDA regulations.¹⁸⁷ Thousands of patients have received treatment under this mechanism over the years under large-scale open label protocols.¹⁸⁸ Under both types of open label protocols, the sponsor must record and report safety data to FDA as part of the NDA.¹⁸⁹

7. Compassionate Use IND

Although the lay public frequently refers to various expanded access programs as “compassionate use,” the term itself is not defined in any FDA regulations or policies.¹⁹⁰ Although broad and undefined, the term has nonetheless appeared in varying contexts at FDA

¹⁸⁵ *Id.*

¹⁸⁶ *Id.* See also HUTT, MERRILL & GROSSMAN, *supra* note 63 at 656.

¹⁸⁷ HUTT, MERRILL & GROSSMAN, *supra* note 63, at 656..

¹⁸⁸ See *Clinical Trial Subjects: Adequate FDA Protections?*, *supra* note 183, at 60-61 (Statement of Dr. Michael A. Friedman, MD) (describing large scale protocols for anti-retroviral drugs in which tens of thousands of patients were enrolled).

¹⁸⁹ See HUTT, MERRILL & GROSSMAN, *supra* note 63 at 656.

¹⁹⁰ See *Clinical Trial Subjects: Adequate FDA Protections?*, *supra* note 183, at 57 (Statement of Dr. Michael A. Friedman, MD).

since 1962.¹⁹¹ While the term “compassionate IND” sometimes appears to be synonymous with an “open protocol,”¹⁹² other sources indicate that a “compassionate use study” existed informally within FDA as early as 1968, conducted under either an existing or separate IND.¹⁹³ Such studies were not formal controlled trials, and permitted use of an investigational drug by either a single patient or a small group, or “for an early exploration of a novel idea.”¹⁹⁴

8. Orphan Drug IND

Prior to 1983, when Congress enacted the Orphan Drug Act,¹⁹⁵ pharmaceutical manufacturers had few incentives to develop drugs for diseases affecting small patient populations.¹⁹⁶ Rational business decisions encouraged development of pharmaceuticals intended to treat a large number of patients, for which mass marketing would overcome the high costs of research and development.¹⁹⁷ Often, even when a compound was thought to be useful in combating rare diseases, the high costs of bringing the drug to market would result in an “orphan drug,” lacking any sponsor willing to conduct the required animal and human clinical trials.¹⁹⁸ Even when sponsors were willing to invest in the necessary research, small patient populations

¹⁹¹ See HUTT, MERRILL & GROSSMAN, *supra* note 63, at 656. A search on FDA’s website for the exact phrase “compassionate use” uncovers more than 1,000 results.

¹⁹² H.R. REP. NO. 97-840, at 11 (2d Sess. 1982).

¹⁹³ See *Clinical Trial Subjects: Adequate FDA Protections?*, *supra* note 183, at 58-59 (Statement of Dr. Michael A. Friedman, MD)

¹⁹⁴ *Id.*

¹⁹⁵ Orphan Drug Act of 1983, Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C. §§ 360aa-ee (2006)).

¹⁹⁶ See generally, David Duffield Rohde, *The Orphan Drug Act: An Engine of Innovation? At What Cost?*, 55 FOOD & DRUG L.J. 125, 126 (2000).

¹⁹⁷ *Id.* See also Patricia J. Kenney, *The Orphan Drug Act – Is it a Barrier to Innovation? Does it Create Unintended Windfalls?*, 43 FOOD DRUG COSM. L.J. 667 (1988).

¹⁹⁸ Rohde, *supra* note 196 at 126.

might not support all the necessary FDA testing.¹⁹⁹ Accordingly, orphan drugs before 1983 frequently found themselves on a “continuing IND status that the FDA and the sponsor tacitly agreed would probably be permanent.”²⁰⁰

The Orphan Drug Act added § 528 to the FD&C Act²⁰¹ in 1983, requiring FDA to “encourage the sponsor” of any designated orphan drug to design protocols for clinical investigations that will include “persons...who need the drug to treat the disease or condition and who cannot be satisfactorily treated by available alternative drugs.”²⁰² Reflecting agency practice since 1983, FDA has promulgated regulations allowing treatment use of designated investigational orphan drugs under a treatment IND pursuant to 21 C.F.R. § 312.34.²⁰³

9. Tropical Drug IND

Until relatively recently, FDA rarely approved NDAs for exclusively “tropical” diseases, arguing that no need for such drugs existed in the United States.²⁰⁴ Nonetheless, FDA has long permitted clinical investigations for drugs treating tropical diseases and thus, like the orphan drug INDs, a tropical drug IND often existed indefinitely. Today, increased international travel and immigration has largely eliminated the rationale for not approving NDAs for tropical drugs.²⁰⁵

¹⁹⁹ See HUTT, MERRILL & GROSSMAN, *supra* note 63, at 656-57.

²⁰⁰ *Id.* at 657. See also Lois K. Perrin, *The Catch-22 For Persons With AIDS: To Have or Not To Have Easy Access to Experimental Therapies and Early Approval for New Drugs*, 69 S.CAL. L.REV 105, 119 (1995).

²⁰¹ See 21 U.S.C. § 360dd.

²⁰² *Id.*

²⁰³ See Orphan Drug Regulations, 57 Fed. Reg. 62076 (Dec. 29, 1992) (codified at 21 U.S.C. § 316.40 (2007)).

²⁰⁴ See HUTT, MERRILL & GROSSMAN, *supra* note 63, at 657.

²⁰⁵ *Id.*

10. Special Exception IND

When a patient is ineligible to participate in a controlled clinical trial of an investigational drug, a willing sponsor may request that FDA make a special exception from the IND protocol and allow a particular patient to receive treatment.²⁰⁶ This special exception IND does not appear in any FDA regulation or guidance.²⁰⁷ Because the patient is a special exception falling outside the criteria of any investigations, data from the patient's experience with the investigational treatment are not included in the reported study results.²⁰⁸

Another form of "special exception" serves as a kind of single patient IND for Group C drugs.²⁰⁹ Under this mechanism, clinical investigators may obtain investigational anticancer treatments directly through NCI, rather than filing a new IND with FDA. Drugs available under NCI's special exception mechanism must have succeeded in Phase I trials and NCI requires some evidence of efficacy before the drug is made available to patients.²¹⁰ Patients receiving treatment through the special exception policy must be ineligible for any ongoing clinical investigations and must have availed themselves of any currently available standard treatment before receiving the investigational drug.

IV. RECENT DEVELOPMENTS: PRESSURE TO EXPAND ACCESS

Despite the numerous regulatory mechanisms for expanded access described in the previous section, patient advocacy groups have consistently criticized the reality of access under FDA's policies and called for increased access to investigational treatments.

²⁰⁶ *Id.*

²⁰⁷ *Id.*

²⁰⁸ *Id.*

²⁰⁹ See FOOD AND DRUG ADMIN., REPORT TO CONGRESS, PATIENT ACCESS TO NEW THERAPIES FOR PEDIATRIC CANCER, *supra* note 113, at 15.

²¹⁰ *Id.*

The treatment IND regulations promulgated in the 1980s, which FDA now proposes to revise, have been criticized for failing to significantly expand access.²¹¹ Although initially relatively successful – by 1994, more than thirty experimental drugs and biologicals were made available under treatment IND provisions²¹²—access under these regulations has largely fallen into disuse.²¹³ Practical limitations often prevent access because drugs provided under a treatment IND are generally considered “experimental” and frequently are not covered by third party insurers or by Medicare and Medicaid.²¹⁴ Additionally, the requirement that a drug sponsor actively pursue marketing approval with “due diligence”²¹⁵ can bar access to a drug when a manufacturer decides not to pursue marketing approval even though it has demonstrated proof of both safety and effectiveness.²¹⁶ Other critics contend that the treatment IND provisions have not been administered in a manner consistent with their original purpose. Despite the fact that the regulations advocate availability of promising drugs as early as Phase 2, FDA generally grants IND protocols only when approval is imminent and clinical trials are nearly complete.²¹⁷

FDA’s recently proposed rules arise amidst newly increased pressure for reform from a number of patient advocacy organizations and their allies. Some critics contend that FDA’s lack of specific criteria for obtaining expanded access has led to disparate access to investigational

²¹¹ See Lisa Terrizzi, *The Need for Improved Access to Experimental Drug Therapy: AIDS Activists and Their Call For a Parallel Track Policy*, 4 ADMIN. L.J. 589, 608 (1991).

²¹² See Perrin, *supra* note 200, at 140.

²¹³ See HUTT, MERRILL & GROSSMAN, *supra* note 63 at 654.

²¹⁴ See Dr. Susan Okie, M.D., *Access before Approval – A Right to Take Experimental Drugs?*, 355 NEW ENG. J. MED. 437, 440 (Aug. 3, 2006); Jerome Groopman, *The Right to a Trial?*, THE NEW YORKER, Dec. 18, 2006.

²¹⁵ 21 C.F.R. § 312.34(b)(iv).

²¹⁶ See Perrin, *supra* note 200, at 140 (noting that competition, financial status, and projected marketing demand can all affect a company’s decision to pursue marketing approval.)

²¹⁷ *Id.* at 141.

therapies,²¹⁸ while others contend that a lack of transparency has limited awareness of expanded access availability primarily to physicians and patients in academic medical centers.²¹⁹ One prominent patient advocacy group, the Abigail Alliance for Better Access to Developmental Drugs (Abigail Alliance), alleged that FDA's policies restricting the rights of terminally ill patients to purchase investigational drugs violated a fundamental right of access under the Constitution.²²⁰ Some critics have argued that FDA policies limiting the ability of drug sponsors to charge patients for expanded access deters industry participation in expanded access programs,²²¹ while others maintain that manufacturers should be entirely barred from charging for expanded access.²²² These criticisms have been incorporated variously in citizen petitions, proposed federal legislation, and a lawsuit against FDA.

Although the patient advocacy movement first grew out of responses to the AIDS epidemic, the past decade has seen an explosion in advocacy groups on behalf of cancer patients.²²³ Patients suffering from serious or life-threatening diseases have new access to information about investigational drugs through the Internet, and these patients are able to obtain detailed information about expanded access programs and clinical trials.²²⁴ Yet, for a variety of

²¹⁸ Proposed Rules to Expand Access, *supra* note 1, at 75149, *see also* Nat'l Coalition for Cancer Survivorship (NCCS) & Am. Soc'y of Clinical Oncology, Citizen Pet. to FDA, 1-2 (March 27, 2006) (Docket No. 2006P-0135) [hereinafter NCCS Citizen Pet.].

²¹⁹ Proposed Rules to Expand Access, *supra* note 1, at 75149.

²²⁰ *See* Complaint, *Abigail Alliance v. McClellan*, 2003 WL 23781358, Civil Action No. 1:03CV1601 ¶¶ 30, 32 (D.D.C., filed July 28, 2003).

²²¹ *Id.* at ¶ 15.

²²² *See* NCCS Citizen Pet., *supra* note 218, at 7.

²²³ *See, e.g.,* Joyce Baldwin, *Demand Grows for Early Access to Promising Cancer Drugs*, 94 J. NAT'L CANCER INST. 1668, 1670, (Nov. 20, 2002). *See also* Justin Gillis, *Patients Press Pleas for Cancer Drugs; Experimental Medicine in Short Supply*, WASH. POST., Apr. 7, 2002 at A1.

²²⁴ *See, e.g.,* Thomas Goetz, *Practicing Patients*, N.Y. TIMES MAG. (Mar. 23, 2008) (describing PatientsLikeMe.com, an online community in which patients share experiences with different treatments and compile hard data based on drugs, dosages, and effectiveness in relieving symptoms of illness.) *See also* Cancer Action Now, <http://www.canceractionnow.org> (web site

reasons, the number of expanded access programs available to cancer patients remains quite small.²²⁵ Modern cancer treatments are rarely “pill in a bottle” drugs and frequently involve complicated and personalized biotechnology.²²⁶ Small biotechnology firms on the forefront of cancer research often face serious capacity constraints and cannot afford to provide drugs outside of the expensive clinical trials necessary to gain marketing approval.²²⁷ While FDA expanded access regulations allow distribution outside of clinical investigations, the practical reality of satisfying FDA’s clinical trial requirements often creates insurmountable barriers to expanded access. As a result, cancer advocacy groups, historically lacking the political clout achieved by AIDS activists in the 1980s, have ramped up efforts to increase industry participation in expanded access programs and achieve policy reform at FDA.²²⁸

In June 2003, the Abigail Alliance, together with the Washington Legal Foundation (WLF), submitted a citizen petition to FDA urging the agency to revise the IND regulations codified in part 312 of the Code of Federal Regulations and establish a three tiered approval mechanism to speed terminally ill patients’ access to promising investigational therapies.²²⁹ Arguing that there is a “different risk-benefit tradeoff facing patients who are terminally ill and have no other treatment options” than that facing ordinary patients²³⁰, the Abigail Alliance proposal asked FDA to grant “Tier 1 Initial Approval” for “promising drugs, biologics, and

for patient advocacy group detailing information for terminally ill patients about researching investigational therapies, finding clinical trials or expanded access programs, and navigating the regulatory landscape.)

²²⁵ Gillis, *supra* note 223 at A1.

²²⁶ Telephone Interview with Rick Hamm, Vice President and General Counsel, Dendreon Corp., in Seattle, Wash. (Apr. 4, 2008) (on file with author).

²²⁷ *Id.*

²²⁸ Gillis, *supra* note 223 at A1.

²²⁹ Abigail Alliance & Washington Legal Found., Citizen Pet. to FDA, *In re Tier 1 Approval Program to Expedite the Availability of Lifesaving Drugs* 1 (Jun. 11, 2003) (Docket No. 2003P-0274).

²³⁰ *Id.* at 9.

devices (“drugs”) intended to treat life-threatening diseases with unmet needs.”²³¹ Under the proposal, FDA would have authority to grant Tier 1 approval “based on the results of a Phase 1 trial demonstrating a safety profile sufficient” to support Phase 2 or Phase 3 clinical trials and “initial evidence of effectiveness based on case-history data from a small number of patients.”²³² In order to safeguard patients, drugs made available under Tier 1 Initial Approval would be limited by various marketing restrictions, unique labeling requirements, and informed consent requirements. Further, in order to protect and encourage further investigation for a drug’s safety and effectiveness, Initial Approval would be contingent on the manufacturer’s continued pursuit of higher tiers of approval and sponsors would only be able to provide the drug to patients found ineligible for or denied access to ongoing clinical trials.²³³ Abigail Alliance asked FDA to revise the treatment IND regulations in order to specifically account for the “risk of illness, injury, or death from [a life-threatening or serious] disease in the absence of the drug” when determining whether or not to make treatment use available.²³⁴

FDA never responded to the Abigail Alliance petition, but did respond to earlier submissions, noting that the Alliance proposal “raised several important questions about expanded access that...deserve further consideration” and expressing doubt that the Alliance proposal “would have the intended desirable effects for patients.”²³⁵ Agency officials found a “significant range of opinion within the patient and provider communities” regarding necessary premarketing standards, noting that others within the cancer patient community have suggested

²³¹ *Id.* Tiers 2 and 3 would consist of “Accelerated Approval” and “Full Approval,” respectively, both already existing in current FDA regulations.

²³² *Id.* at 5.

²³³ *Id.* at 5-6.

²³⁴ *Id.* at 4.

²³⁵ Letter from Peter J. Pitts, Associate Commissioner for External Relations, Department of Health and Human Services, to Frank Burroughs, President, Abigail Alliance for Better Access to Developmental Drugs 3 (Apr. 25, 2003).

that “FDA needs a strong clinical trial system as the basis of the approval of cancer drugs....”²³⁶

On the grounds that the Abigail Alliance proposal would not provide sufficient statistical information to determine “a reasonably precise estimate of response rate” or “enough experience to detect serious adverse effects,”²³⁷ FDA concluded that the Alliance proposal failed to strike an appropriate balance between the potential benefits of early access to investigational drugs and the risks of marketing drugs without knowledge of potential clinical benefits or toxicity.²³⁸

Lacking a formal response to the petition, the Abigail Alliance and WLF filed a lawsuit against FDA in the United States District Court for the District of Columbia, alleging that FDA’s policy of prohibiting the sale of investigational drugs showing early evidence of safety and effectiveness to terminally ill patients violated the U.S. Constitution’s Fifth Amendment guarantee against deprivation of life without due process of law.²³⁹ The district court dismissed the case for failure to state a cause of action, holding that “there is no constitutional right of access to unapproved drugs.”²⁴⁰ A divided panel of the United States Court of Appeals for the District of Columbia reversed the lower court’s decision, holding that “where there are no alternative government-approved treatment options, a terminally ill, mentally competent adult patient’s informed access to potentially life-saving investigational new drugs determined by the FDA after Phase I trials to be sufficiently safe for expanded human trials warrants protection under the Due Process Clause.”²⁴¹ The majority applied the Supreme Court’s test for substantive

²³⁶ *Id.* at 4.

²³⁷ *Id.*

²³⁸ *Id.* at 5.

²³⁹ Complaint, *Abigail Alliance v. McClellan*, supra note 220 at ¶¶ 30, 32.

²⁴⁰ *Abigail Alliance for Better Access to Developmental Drugs v. McClellan*, No. 03-1601, 2004 WL 3777340, at *1 (D.D.C. Aug. 30, 2004).

²⁴¹ *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 445 F.3d 470, 486 (D.C. Cir. 2006) [hereinafter *Abigail I*].

due process claims enumerated in *Washington v. Glucksberg*,²⁴² in which courts, after carefully stating the asserted liberty interest, must inquire whether the interest at issue is objectively “deeply rooted in this Nation’s history and tradition,” and “implicit in the concept of ordered liberty[.]”²⁴³ The majority evaluated the history of new drug regulation in light of “our Nation’s history, legal traditions, and practices”²⁴⁴ and found that the history of governmental regulation of access to new drugs was relatively recent and that “[f]or over half of our Nation’s history...until the enactment of the 1906 Act, a person could obtain access to any new drug without any government interference whatsoever.”²⁴⁵ The appellate panel therefore found the Abigail Alliance’s carefully crafted liberty interest constituted a fundamental right, subjecting any governmental infringement against this liberty interest to strict scrutiny. Because the district court never reached the issue of whether the FDA’s policy violated this fundamental liberty interest, the panel remanded the case back to the district court to determine “whether the FDA’s policy barring access to post-Phase I investigational new drugs by terminally ill patients is narrowly tailored to serve a compelling governmental interest.”²⁴⁶

²⁴² 521 U.S. 702, 710 (1997).

²⁴³ *Id.* at 721 (quoting *Moore v. City of East Cleveland*, 431 U.S. 494, 503 (1977); *Snyder v. Massachusetts*, 291 U.S. 97 (1934)).

²⁴⁴ *Id.*, (quoting *Palko v. Connecticut*, 302 U.S. 319, 325-26 (1937)).

²⁴⁵ *Abigail I*, 445 F.3d at 483. A detailed recounting of the substantive due process analysis applied in the *Abigail* cases goes beyond the scope of this paper and can be found in numerous other sources. See, e.g., Won Bok Lee, *Abigail Alliance v. von Eschenbach: Constitutional Rights of Terminally Ill Patients Reconsidered*, 36 L.J. MED. & ETHICS 391 (Spring 2008); *Majority Upholds Restrictions on Access to Experimental Drugs*, 26 BIOTECHNOLOGY L. REP. 469 (2007); Stephen R. Kovatis, *The Right to Live: Do the Terminally Ill Have a Constitutional Right to Use Experimental Drugs? Abigail Alliance v. von Eschenberg*, 445 F.3d 470 (D.C. Cir. 2006), 26 J. SCI. TECH. & ENVTL. L. 149 (Spring 2007)

²⁴⁶ *Abigail I*, 445 F.3d at 486.

The panel's ruling, viewed as a major victory for cancer patient advocates, undoubtedly spurred FDA's decision to revise the IND regulations on its own terms.²⁴⁷ The ruling itself, however, would prove to be short-lived. FDA petitioned the D.C. Circuit for a rehearing *en banc* and the full D.C. Circuit reversed the panel's decision.²⁴⁸ On rehearing, the majority framed the Alliance's claimed liberty interest as a "fundamental right of access for the terminally ill to experimental drugs,"²⁴⁹ a wider interest than the one stated by the three-judge panel in *Abigail I*. Further, the *Abigail II* court engaged in a detailed and lengthy analysis of historical regulation of drugs, finding traditions dating back as far as 15th century England and colonial times.²⁵⁰ Concluding that the historical regulation of drugs affirmatively showed a longstanding tradition of governmental control over access to drugs, and discarding a number of common law doctrines advanced by the Abigail Alliance, the court held that the "Alliance's claimed right is not fundamental [and therefore] subject only to rational basis scrutiny,"²⁵¹ under which the Alliance must show that FDA's policy bears no rational relationship to a legitimate state interest.²⁵² Because restricting access to investigational drugs is rationally related to the agency's interest in protecting all patients from potentially unsafe drugs with unknown therapeutic effects, the court affirmed the district court's dismissal. The *Abigail II* court emphasized that the Alliance's claims

²⁴⁷ See, e.g., Okie, *supra* note 214, (quoting William Schultz, former deputy commissioner for policy at FDA, describing the ruling as "a huge, huge, devastating decision".) See also George J. Annas, *Cancer and the Constitution: Choice at Life's End*, 357 NEW ENG. J. MED. 408, (Jul. 26, 2007) ("In direct response to *Abigail Alliance*, the FDA proposed amending its rules to encourage more drug companies to offer their investigational drugs through compassionate use programs."); Groopman, *supra* note 214, ("The opinion...shocked legal scholars and officials at the F.D.A.,....The agency, determined not to cede control of drug regulation to Congress or the courts, intends to release some of the proposals for public comment....").

²⁴⁸ See *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007) (*en banc*), *cert. den'd* 128 S.Ct. 1069 (2008) [hereinafter *Abigail II*].

²⁴⁹ *Id.* at 703.

²⁵⁰ *Id.* at 703-706.

²⁵¹ *Id.* at 712 (citing *Glucksberg*, 521 U.S. at 722).

²⁵² *Id.*

could all “be aired in the democratic branches, without injecting the courts into unknown questions of science and medicine” and that the court’s holding would ensure that the “debate among the Alliance, the FDA, the scientific and medical communities, and the public may continue through the democratic process.”²⁵³

The Abigail Alliance has also attempted to change FDA policies through federal legislation. In 2005, Sens. Sam Brownback and Tom Inhofe introduced legislation during the that would create a new approval process for access to investigational drugs for treatment use, building on the three tiered approval mechanism set forth in the 2003 Abigail Alliance citizen petition.²⁵⁴

The Access, Compassion, Care, and Ethics for Seriously Ill Patients Act (ACCESS Act) began by stating a series of congressional findings, including that “[t]he necessity of placebo controlled studies has been questioned on both scientific and medical grounds for seriously ill patients”²⁵⁵ and that “[s]eriously ill patients have a right to access available investigational drugs, biological products, and devices.”²⁵⁶ Like the citizen petition, the ACCESS Act sought to create a “Tier 1 approval” process for drugs with available Phase I safety data and preliminary evidence of effectiveness for treatment of a serious or life-threatening disease.²⁵⁷ The Act specifically denotes that such evidence can be based on “uncontrolled data such as case histories, information about the pharmacological mechanism of action, data from animal and computer models” and other information not tied to traditional placebo-controlled clinical investigations.²⁵⁸

²⁵³ *Id.* at 713.

²⁵⁴ Access, Compassion, Care, and Ethics for Seriously Ill Patients Act (ACCESS Act), S. 1956 & H.R. 6303, 109th Cong. (2005).

²⁵⁵ *Id.* at § 2(1).

²⁵⁶ *Id.* at § 2(4).

²⁵⁷ *Id.* at § 3(b)(1)(A). (i)-(ii).

²⁵⁸ *Id.* at § 3(b)(1)(A)(ii).

A sponsor seeking Tier 1 approval would need to provide assurance that it would continue clinical investigations designed to obtain Tier 3 full approval.²⁵⁹ FDA would then either approve the application or refer the application to an Accelerated Approval Advisory Committee.²⁶⁰

In order to obtain access to the drug, patients would provide written informed consent, waive any right to sue the drug manufacturer or sponsor, and consent to provide data to the manufacturer about the patient and the patient's use of the treatment.²⁶¹ In an effort to protect clinical trials while preserving the right of patients to receive investigational treatments, the Act would require FDA to prohibit placebo-only or no-treatment-only concurrent controls in any clinical investigation of treatments for serious or life-threatening diseases for which no reasonably effective alternatives exist.²⁶²

The bill was referred to the Committee on Health, Education, Labor and Pensions, but the 109th Congress ended without any action taken on the legislation. The bill has not since been revived.

In March 2006, the National Coalition for Cancer Survivorship (NCCS) and the American Society for Clinical Oncology (ASCO) filed a separate citizen petition with FDA.²⁶³ The NCCS petition requested that the agency issue guidance clarifying the circumstances under which expanded access programs may be initiated, recognizing that FDA's regulations provide "ample authority for the conduct of expanded access programs" but noting that "there is uncertainty about the procedures and standards applicable to such programs."²⁶⁴ The petition emphasized that expanded access programs should not interfere with ongoing clinical trials or

²⁵⁹ *Id.* at § 3(b)(1)(A)(iii).

²⁶⁰ *Id.* at § 3(b)(2).

²⁶¹ *Id.* at § 3(b)(5)(B).

²⁶² *Id.* at § 4.

²⁶³ NCCS Citizen Pet., *supra* note 218.

²⁶⁴ *Id.* at 1.

delay marketing approval, and recommended FDA adopt a systematic approach to providing access.²⁶⁵ With regard to single patient access, NCCS recommended that FDA design standard protocols and model consent forms in order to ease the burden on sponsors and physicians, who, under current regulations, must process each application individually.²⁶⁶ The petition also sought to clarify the criteria FDA would use in order to determine when expanded access could be made available prior to Phase 3 or, in unusual circumstances, prior to Phase 2. The petition suggested that FDA should rely on a number of different variables, such as the nature and strength of the evidence of safety and effectiveness, unmet patient need, the likelihood and imminence of marketing approval, and the likely availability of the drug itself.²⁶⁷ In evaluating effectiveness, the petition urged FDA to focus on the quality of responses to a drug – e.g., whether some responses appear particularly durable or are accompanied by significant relief of cancer-related symptoms – rather than pure statistical endpoints.²⁶⁸ The proposal also noted that many manufacturers are limited by capacity constraints, and urged FDA to permit greater access to drugs where “the agent in question is a small molecule with relatively straightforward manufacturing process and cost” as opposed to a “more complex biological product[.]”²⁶⁹ In contrast to the position taken by the Abigail Alliance, the NCCS petition argued that FDA should “urge sponsors to forgo cost recovery and provide drugs without charge to patients in expanded access,” noting that this has been “[t]he custom among sponsors” and would “appear to be the preferable practice by far.”²⁷⁰ FDA has not responded to the NCCS petition.

²⁶⁵ *Id.* at 4.

²⁶⁶ *Id.* at 3.

²⁶⁷ *Id.* at 5.

²⁶⁸ *Id.*

²⁶⁹ *Id.*

²⁷⁰ *Id.* at 7.

V. FDA'S PROPOSED REGULATIONS

On December 14, 2006, FDA proposed two new regulations in the Federal Register addressing expanded access to investigational drugs for treatment use and charging for investigational drugs.²⁷¹ The expanded access proposal would amend FDA's IND regulations by replacing the current sections on treatment use, revising regulations on clinical holds, and adding a new "Subpart I" on expanded access.²⁷² The charging proposal would remove the current provisions in § 312.7(d) and create a new § 312.8 describing general requirements for charging for investigational drugs, specific requirements for charging for investigational drugs in a clinical trial, charging for investigational drugs under the new Subpart I, and requirements for determining what costs may be recovered when charging for an investigational drug.²⁷³

A. Expanded Access to Investigational Drugs

According to FDA, the proposed expanded access regulations are intended to address the concerns that motivated congress to include § 561 of the FD&C Act in the 1997 FDAMA legislation. Specifically, the rules are intended to address concerns about inconsistent application of access policies and inequitable access for patients outside of academic medical research centers.²⁷⁴ The proposed regulations are intended to detail and clarify the various available procedures as well as the criteria, submission requirements, and safeguards employed for each method of access.²⁷⁵ FDA maintains that increased awareness of available expanded access problems will make investigational drugs more widely available "in appropriate situations," and

²⁷¹ Proposed Rules to Expand Access, *supra* note 1; Proposed Rules for Charging, *supra* note 2.

²⁷² Proposed Rules to Expand Access, *supra* note 1, at 75150.

²⁷³ Proposed Rules for Charging, *supra* note 2, at 75171.

²⁷⁴ Proposed Rules to Expand Access, *supra* note 1, at 75149.

²⁷⁵ *Id.*

argues that clearly articulated administrative procedures will ease the burden on sponsors and physicians making investigational drugs available for individual patient use and “result in more patients with serious or immediately life-threatening diseases or conditions getting the earliest possible access” to investigational therapies.²⁷⁶

The proposed regulations establish specific criteria for all expanded access uses and would permit expanded access for individual patients, intermediate-size patient populations, and larger patient populations.

1. Requirements for All Expanded Access Use

In all circumstances where expanded access use is permitted, FDA would require that the patient or patients seeking treatment have a “serious or immediately-life threatening disease or condition” with no comparable or satisfactory alternative therapy.²⁷⁷ FDA would need to determine that the potential patient benefit justifies the potential risks of treatment use, and that

²⁷⁶ *Id.* at 75149-75150.

²⁷⁷ *Id.* at 75150-75151. Because of “the difficulty of specifically describing the criteria that characterizes a ‘serious disease or condition,’” the proposal does not provide a definition but rather points to other agency documents in which the term is described. *See* FDA Guidance for Industry, Fast Track Drug Development Programs – Designation, Development, and Application Review, 63 Fed. Reg. 64093 (Nov. 18, 1998). FDA suggests that the term applies to conditions that have “an important effect on functioning,” such as stroke, schizophrenia, or rheumatoid arthritis, or have important effects on “other aspects of quality of life,” such as chronic depression or seizures. *See* Proposed Rules to Expand Access, *supra* note 1 at 75151. The proposed rules define “immediately life-threatening” as “a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.” *Id.* at 75166; proposed 21 C.F.R. § 312.300(b). FDA states that a “lack of comparable or satisfactory therapeutic alternatives” ordinarily means either no available therapy to treat the patient’s condition exists, or that the patient has tried available therapies and either failed to respond adequately or proved intolerant to them. Generally, “available” refers only to FDA-approved products labeled for treatment for the patient’s disease or condition, but in some cases could refer either to treatment not regulated by FDA, such as surgery, or off-label use supported by “compelling literature evidence.” *Id.* at 75151. *See also* FDA Guidance for Industry, Available Therapy, 69 Fed. Reg. 44039 (July 23, 2004).

any potential risks are not “unreasonable in the context of the disease or condition” at issue.²⁷⁸

Lastly, expanded access use could not interfere with clinical investigations that might support full marketing approval, or “otherwise compromise the potential development” of the investigational drug.²⁷⁹

Under the proposal, the specific amount of evidence necessary to show safety and effectiveness for expanded access use varies depending on the type of expanded access program under which the drug is provided, and is described separately in those provisions. In general, the amount of evidence necessary would depend on the size of the patient population to be treated and relative seriousness of the disease or condition for which treatment is sought.²⁸⁰ Thus, treatment of a large number of patients under a treatment IND would require greater evidence than treatment for only a small number of patients, while intermediate-size patient populations would fall somewhere in between.²⁸¹ In addition to the size of the patient population, FDA would consider authorizing expanded access on less data based on the seriousness of the disease. For example, the proposal states that, for treatment of an individual patient facing an immediately life-threatening condition, the agency would “ordinarily” require completed Phase I safety testing of the drug along with “preliminary evidence suggesting possible effectiveness” to support expanded access use.²⁸² The proposal suggests that in some cases access could be based on “preclinical data or on the mechanism of action.”²⁸³ Where larger patient populations are

²⁷⁸ Proposed Rules to Expand Access, *supra* note 1, at 75151; proposed 21 C.F.R. § 312.305(a)(2).

²⁷⁹ *Id.*; proposed 21 C.F.R. § 312.305(a)(3).

²⁸⁰ *Id.*

²⁸¹ *Id.* The new proposal continues the use of the terms “treatment IND” or “treatment protocol” for expanded access programs making investigational drugs available to large patient populations for treatment use.

²⁸² *Id.*

²⁸³ *Id.*

involved, FDA would ordinarily require data from Phase 3 clinical trials to support expanded access use under a treatment IND or treatment protocol where the condition is serious but not “imminently life threatening,” and “might permit” treatment for an “immediately life-threatening” disease based on “compelling data from phase 2 trials.”²⁸⁴

As under current regulations, the proposed rule would require submission of a new IND or an amendment to an existing IND before patients obtain access to an investigational treatment,²⁸⁵ and describes the necessary contents of the application.²⁸⁶ The proposal sets forth the requirements and responsibilities of sponsors and investigators,²⁸⁷ and provides that expanded access would be allowed to begin thirty days after receipt of a newly submitted IND, or upon earlier notification from FDA. Expanded access under an existing IND would ordinarily begin immediately upon submission of the expanded access protocol.²⁸⁸

2. Expanded Access for Individual Patients

In addition to the criteria applicable to all expanded access uses, the proposed regulations detail specific criteria for different expanded access uses. Proposed § 312.310 describes the requirements for individual patient expanded access. Under the rule, an individual patient may be permitted to obtain expanded access use of an investigational drug through a licensed physician

²⁸⁴ *Id.*

²⁸⁵ *Id.* at 75151-75152; proposed 21 C.F.R. § 312.305(b)(1).

²⁸⁶ *Id.* at 75152; proposed 21 C.F.R. § 312.305(b)(2)-(3).

²⁸⁷ *Id.*; proposed 21 C.F.R. § 312.305(c).

²⁸⁸ *Id.*; proposed 21 C.F.R. § 312.305(d). The proposed rule contains two exceptions about when access may begin. First, proposed § 312.305(d)(2)(i) provides that treatment of an individual patient in an emergency situation may begin upon authorization by a FDA reviewing official. Second, proposed § 312.305(d)(2)(ii) requires a 30-day wait to begin any Treatment IND or treatment protocol use even if an existing IND is on file with FDA, in order to build in sufficient time for the agency to review proposed expanded access use that can potentially affect large numbers of patients.

if the physician determines that the probable risk to the patient from use of the drug is not greater than the probable risk from the relevant disease or condition,²⁸⁹ and FDA determines that the patient was unable to receive access through another type of IND, such as a clinical trial.²⁹⁰ Either the drug sponsor or the patient’s licensed physician can apply for expanded access if an IND is currently effective.²⁹¹ A drug sponsor would be required to submit a protocol under an existing IND, whereas a physician would file a new IND under a “right of reference” to the sponsor’s IND along with additional specific information about the patient.²⁹² The proposed rules would limit expanded access treatment of an individual patient to a “single course of therapy for a specified duration” absent FDA authorization for multiple courses or chronic therapy.²⁹³ Consistent with current regulations, the proposed rules set out emergency procedures for expanded access use for individual patients.²⁹⁴ In an emergency situation requiring treatment of an individual patient prior to filing an IND, FDA could authorize the expanded access use by telephone, facsimile, or other electronic communication.²⁹⁵ The drug sponsor or physician would thereafter be obligated to file a written submission complying with all the requirements of proposed § 312.305 and § 312.310 within five working days of FDA’s authorization.²⁹⁶

²⁸⁹ *Id.* at 75153; proposed 21 C.F.R. § 312.310(a)(1).

²⁹⁰ *Id.*; proposed 21 C.F.R. § 312.310(a)(2).

²⁹¹ *Id.*; proposed 21 C.F.R. § 312.310(b).

²⁹² *Id.*

²⁹³ *Id.*; proposed 21 C.F.R. § 312.310(c). The rules further allow FDA to require a sponsor to monitor extended individual patient expanded access use, and would require the sponsor or physician to provide FDA with a written summary of the results of the treatment use, including any unexpected adverse events. *Id.*; proposed 21 C.F.R. § 312.310(c)(2)-(3). A “significant number of similar requests” for individual access – such as, perhaps, ten requests for the same treatment within six months -- may cause FDA to request the sponsor to submit a protocol under § 312.315 or § 312.320 of the proposed rules.

²⁹⁴ *Id.*; proposed 21 C.F.R. § 312.310(d).

²⁹⁵ *Id.* at 75154; proposed 21 C.F.R. § 312.310(d)(1).

²⁹⁶ *Id.*; proposed 21 C.F.R. § 312.310(d)(2). FDA insists that such emergency use will be limited only to “true emergencies” in which there is no time to file a prior written submission, and notes

3. Expanded Access for Intermediate Size Patient Populations

FDA has also proposed rules governing “intermediate-size patient populations,” intended to include groups of patients “smaller than those typical in treatment INDs or treatment protocols.”²⁹⁷ The agency could ask a sponsor to provide access under this section where the agency has received a “significant number of requests” for individual patient access.²⁹⁸ FDA proposes that this type of expanded access would apply where a drug is not being developed for marketing but nonetheless represents the only promising therapy for a rare disease or condition,²⁹⁹ where a drug is being developed but patients ineligible to participate in clinical investigations seek access to the drug,³⁰⁰ or where an approved drug is no longer marketed.³⁰¹

The specific criteria described in this section would apply to expanded access use for intermediate-size patient populations in addition to the criteria applicable to all expanded access uses.³⁰² In order to permit expanded access under this section, FDA would first need to find “enough evidence that the drug is safe at the dose and duration proposed for expanded access use

that FDA’s experience with emergency use indicates that a follow-up written submission is rarely provided after emergency use is obtained. *Id.*

²⁹⁷ *Id.*; proposed 21 C.F.R. § 312.315.

²⁹⁸ *Id.*

²⁹⁹ *Id.*; proposed 21 C.F.R. § 312.315(a)(1).

³⁰⁰ *Id.*; proposed 21 C.F.R. § 312.315(a)(2). Patients may not be eligible for clinical trials because they have a different disease or stage of disease from the one under investigation, or do not otherwise meet particular enrollment criteria; because enrollment in the trial is closed; or because the trial site is too geographically inaccessible for the patient. *Id.*

³⁰¹ *Id.*; proposed 21 C.F.R. § 312.315(a)(3). An approved drug might cease to be marketed for safety reasons or for failure to meet conditions of the drug approval, 21 C.F.R. § 312.315(a)(3)(i), or because the drug contains the same active moiety as an approved drug product that is unavailable for marketing, 21 C.F.R. § 312.315(a)(3)(ii). Where the drug is not available due to safety concerns, the rules provide that a subset of patients may exist for whom the benefits of treatment use outweigh the potential safety risks. *See Proposed Rules for Expanded Access, supra* note 1, at 75154, proposed 21 C.F.R. § 312.315(a)(3)(i).

³⁰² Proposed Rules to Expand Access,, *supra* note 1, at 75154.; proposed 21 C.F.R. § 312.315(b).

to justify a clinical trial of the drug” for the number of patients expected to receive expanded access use of the drug,³⁰³ and “at least preliminary clinical evidence of effectiveness” or of a “plausible pharmacological effect” of the drug to make expanded access use a “reasonable therapeutic option” for the proposed patient population.³⁰⁴

Intermediate patient-size IND applications would need to specify whether or not the drug is being developed and would describe the population to be treated.³⁰⁵ If the drug is not being actively developed, the sponsor must fully explain why the drug cannot be developed and what circumstances would be necessary for development.³⁰⁶ If the drug is not being investigated in clinical trials, the sponsor must explain why patients cannot be enrolled in a trial, and what circumstances would be necessary to conduct clinical trials in the relevant patients.³⁰⁷ FDA would annually review expanded access programs for intermediate-size populations in order to determine whether continued use is appropriate.³⁰⁸ The drug sponsor would be responsible for monitoring expanded access protocols in order to ensure that physicians comply both with the protocol and all regulations applicable to investigators.³⁰⁹

³⁰³ *Id.*; proposed 21 C.F.R. § 312.315(b)(1). As in the traditional model of drug development, FDA requires more data about an investigational treatment as the number of patients exposed to potential risks increases. Therefore, more clinical experience is required for an intermediate-size patient population than would be for individual patient expanded access. *Id.* at 75154.

³⁰⁴ *Id.*; proposed 21 C.F.R. § 312.315(b)(2).

³⁰⁵ *Id.*; proposed 21 C.F.R. § 312.315(c)(1).

³⁰⁶ *Id.*; proposed 21 C.F.R. § 312.315(c)(2).

³⁰⁷ *Id.*; proposed 21 C.F.R. § 312.315(c)(3).

³⁰⁸ *Id.* at 75155; proposed 21 C.F.R. § 312.315(d)(1). For instance, if the drug is not being developed, the agency will consider whether clinical studies are possible to develop the drug for marketing. Proposed 21 C.F.R. § 312.315(d)(1)(i). If the drug is being actively developed, FDA will consider whether the expanded access use is interfering with ongoing investigations. Proposed 21 C.F.R. § 312.315(d)(1)(ii). If the patient population increases in size, FDA will consider whether the sponsor should provide treatment under a treatment IND or treatment protocol under proposed § 312.320. Proposed 21 C.F.R. § 312.315(d)(1)(iii).

³⁰⁹ Proposed Rules for Expanded Access, *supra* note 1 at 75155; proposed 21 C.F.R. § 312.315(d)(2).

3. Expanded Access Under a Treatment IND or Treatment Protocol

A treatment IND or treatment protocol would be used for widespread treatment use of an investigational drug and would likely apply to populations in excess of one hundred patients.³¹⁰ The proposed rules largely mirror the mechanisms currently available under §§ 312.34 and 312.35 of the C.F.R.³¹¹ Consistent with current treatment IND regulations, the proposed rules would permit access under a treatment IND or protocol only if the drug is being investigated under controlled clinical trials under an IND intended to support marketing approval for the proposed treatment use³¹² or all clinical trials for the drug are complete.³¹³ As under current regulations, the sponsor would need to be “actively pursuing marketing approval” for the proposed expanded access use with due diligence.³¹⁴

To authorize treatment of a “serious disease or condition,” the proposed rule would require “sufficient clinical evidence of safety and effectiveness” to support the proposed use, ordinarily consisting of data from phase 3 trials, but for which compelling data from completed phase 2 trials could suffice.³¹⁵ For an “immediately life-threatening” disease or condition, available scientific evidence, taken as a whole, would need to provide a reasonable basis to conclude that the investigational drug may be effective for the proposed use and would not expose patients to an “unreasonable and significant risk” of harm. The proposal suggests this

³¹⁰ See *id.* at 75154.

³¹¹ See *supra*, notes 150 to 154 and accompanying text.

³¹² Proposed Rules to Expand Access, *supra* note 1, at 75155; proposed 21 C.F.R. § 312.20(a)(1)(i).

³¹³ *Id.*; proposed 21 C.F.R. § 312.20(a)(1)(ii).

³¹⁴ *Id.*; proposed 21 C.F.R. § 312.20(a)(2).

³¹⁵ *Id.*; proposed 21 C.F.R. § 312.20(a)(3)(i).

data would ordinarily consist of clinical data from Phase 3 or Phase 2 trials, but could potentially be based on “more preliminary clinical evidence.”³¹⁶

In addition to specific submission requirements under this section³¹⁷, the proposed rules would also obligate the drug sponsor to monitor the treatment protocol and ensure that all physicians administering treatment comply with both the protocol and all applicable regulations.³¹⁸

The preamble to the proposed rule addresses FDA’s concerns that drug sponsors may use “open-label safety studies” to make investigational drugs available to seriously ill patients instead of the treatment IND procedures.³¹⁹ While the goal of an open-label safety study is to “better characterize the safety of a drug late in its development,” many such studies bear characteristics resembling treatment INDs. FDA states that the agency would consider reclassifying some open label studies as a treatment protocol, particularly where a study provides “broad access to an investigational drug in the later stages of development, but lacks planned, systematic data collection and a design appropriate to evaluation of a safety issue[.]”³²⁰ FDA insists such studies should fall under the treatment IND procedure in order to ensure a “more formal review process” that will specifically evaluate the impact of the expanded access treatment on both enrollment in clinical trials and the overall progress of the drug’s development.³²¹ FDA further notes that the continuation phase of a clinical trial, in which participants in the trial who received a placebo are permitted access to the investigational drug,

³¹⁶ *Id.*; proposed 21 C.F.R. § 312.20(a)(3)(ii).

³¹⁷ *Id.*; proposed 21 C.F.R. § 312.320(b) (requiring information adequate to satisfy FDA that the general criteria for expanded access use and those specific to the treatment IND or treatment protocol have been met.)

³¹⁸ *Id.*; proposed 21 C.F.R. § 312.320(c).

³¹⁹ *Id.* at 75155.

³²⁰ *Id.*

³²¹ *Id.*

would not be reclassified as a treatment IND because it is limited exclusively to clinical trial participants.³²²

B. Charging for Investigational Drugs

FDA has also proposed new regulations governing charging for investigational drugs.³²³ The agency has advanced three principal reasons for revising the charging regulations. First, FDA notes that the current regulations in § 312.7(d) failed to anticipate the high number of requests to charge for use of a third party's approved drug in a clinical trial, rather than a sponsor's own investigational drug.³²⁴ Second, the current charging regulations only specify conditions to charge under a treatment IND or treatment protocol; the new rules would include authority to charge for the two "new" categories of expanded access in proposed section 312.300.³²⁵ Last, FDA maintains that the current charging rule lacks specificity regarding the types of costs that can be recovered. The agency therefore intends to provide clearer guidance to drug sponsors by specifying the "costs appropriate for recovery" in treatment use as opposed to clinical trials.³²⁶

1. General Requirements for Charging

Under all circumstances in which a sponsor intends to charge for access to an investigational drug – either in a clinical trial or as part of an expanded access program – FDA

³²² *Id.* at 75155-75156.

³²³ *See* Proposed Rules for Charging, *supra* note 2.

³²⁴ *Id.* at 75169. Drug sponsors might to charge for a third party's approved drug for use as an active control, or in combination with the sponsor's drug. Third parties conducting off-label use studies, or comparing the effectiveness of various drugs, might also seek to charge for drugs during clinical investigations.

³²⁵ *Id.*

³²⁶ *Id.* at 75169-75170.

would require the sponsor to comply with specific requirements for the relevant type of use, provide justification that the amount to be charged reflects only costs for which recovery is permissible, and obtain prior written authorization from the agency.³²⁷

2. Charging in a Clinical Trial

The preamble to the proposed rule specifies that FDA will require “exceptional circumstances” in order to justify charging in a clinical trial because the costs of an investigational drug in trial should be considered an anticipated cost of development.³²⁸ Under the proposal, a sponsor that seeks to charge for its own drug in a clinical trial would need to provide evidence that the potential benefit of the drug under investigation would represent a significant therapeutic advantage over available products, demonstrate that the data to be obtained in the clinical trial are essential to establishing the drug’s safety and effectiveness for initial approval (or to support a “significant change in the labeling” of an approved drug), and demonstrate that the extraordinary cost of the drug requires charging in order to continue clinical development of the drug.³²⁹

FDA has articulated different criteria, however, where a drug sponsor seeks to charge for an approved drug obtained from another entity for use in clinical testing. FDA intends to establish a lower threshold requirement where a sponsor seeks to use another entity’s approved drug as an active control, or in combination with another drug, during clinical investigations.

³²⁷ *Id.* at 75180, proposed 21 C.F.R. § 312.8(a)(1). The new proposal requiring written authorization from FDA in order to charge changes the current treatment IND authorization, under which a sponsor could charge automatically 30 days after submission. FDA intends to review applications carefully to ensure compliance with all applicable criteria and that only permissible costs are recovered. *Id.*

³²⁸ *Id.* at 75170.

³²⁹ *Id.* at 75180; proposed 21 C.F.R. § 312.8(b)(i)-(iii).

Noting ethical concerns about the use of a placebo control in patients during some clinical investigations, and that enrolled patients would otherwise receive the approved drug were they not participating in the clinical trial,³³⁰ FDA would require the sponsor to demonstrate only that the trial is adequately designed to evaluate the safety or effectiveness of the sponsor's drug and that the drug is not being provided to the sponsor free of charge.³³¹ The agency would apply additional criteria to a clinical trial sponsor who seeks to charge for an approved drug obtained from another entity in order to evaluate the drug's safety and effectiveness for an off-label use or to obtain additional safety information.³³²

3. Charging For Expanded Access for Treatment Use

The proposed regulations would also replace the current regulation on charging for investigational drugs through a treatment IND or protocol. The new "subpart I" categories of treatment – expanded access for individual patients and expanded access for intermediate-size patient populations – would be included under the new regulation. The new rule would require any sponsor seeking to charge for a drug available under any of the subpart I categories of expanded access to "provide reasonable assurance" that charging will not interfere with developing the drug for marketing approval.³³³

³³⁰ *Id.* at 75171.

³³¹ *Id.* at 75181; proposed 21 C.F.R. § 312.8(b)(2).

³³² *Id.*; proposed 21 C.F.R. § 312.8(b)(3). In the preamble, FDA notes that the sponsors of post-approval investigations are sponsor-investigators that do not conduct the research for purposes of commercialization and are therefore unlikely to recoup costs by marketing the drug upon approval. *Id.* at 75172.

³³³ *Id.* at 75172, 75181; proposed 21 C.F.R. § 312.2(c)(1).

The agency proposes to require additional criteria before approving requests to charge for expanded access to drugs made available under a treatment IND or treatment protocol.³³⁴ FDA expresses concern that treatment INDs, unlike individual patient access or intermediate-size patient populations, carry particularly strong risks of interference with drug development for marketing approval. FDA has expressed concern that large enrollments in treatment protocols could significantly affect enrollment in clinical trials intended to gauge safety and effectiveness.³³⁵ Thus, the new regulations would require treatment IND sponsors to provide adequate evidence of sufficient enrollment in clinical trials so as to reasonably allow FDA to determine that trials will be completed as planned,³³⁶ as well as evidence of “adequate progress in the development of the drug for marketing approval.”³³⁷ Sponsors would also be required to submit information included in their “general investigational plan”³³⁸ specifying all drug development milestones expected to occur in the coming year.³³⁹

Authorization to charge would be limited only to the number of patients authorized to receive the drug for treatment use³⁴⁰ and would extend for one year (or less, depending on the potential impact on drug development) subject to possible renewal.³⁴¹

4. Recoverable Costs

³³⁴ *Id.* at 75181; proposed 21 C.F.R. § 312.2(c)(2).

³³⁵ *Id.* at 75172.

³³⁶ *Id.* at 75181; proposed 21 C.F.R. § 312.8(c)(2)(i).

³³⁷ *Id.*; proposed 21 C.F.R. § 312.8(c)(2)(ii). Evidence could include “successful meetings with FDA before submission of an [NDA], submission of an NDA, or completion of other significant drug development milestones.” *Id.* at 75172.

³³⁸ *See* 21 C.F.R. § 312.23(a)(3)(iv) (2007).

³³⁹ Proposed Rules for Charging, *supra* note 2, 71 Fed. Reg. at 75181; proposed 21 C.F.R. § 312.8(c)(2)(iii).

³⁴⁰ *Id.*; proposed 21 C.F.R. § 312.8(c)(3).

³⁴¹ *Id.*; proposed 21 C.F.R. § 312.8(c)(4).

Notably, FDA also proposes to revise the kinds of costs a sponsor could recover when charging for an investigational drug.³⁴² Under the proposed rule, sponsors charging for an investigational drug in either a clinical trial or under an expanded access program would be able to recover only the “direct costs” of providing the drug.³⁴³ Direct costs include only those that can be “specifically and exclusively attributed to providing the drug for the investigational use for which FDA has authorized cost recovery.”³⁴⁴ These include costs per unit to manufacture the drug, costs to acquire the drug from another manufacturing source, and direct costs to ship and handle the drug.³⁴⁵ The proposal would not allow recovery for “indirect costs” that are not attributable solely to making the drug available for treatment use, such as expenditures to produce the drug for commercial sale, as well as research and development, administrative, and labor costs.³⁴⁶

The proposed rule includes a few concessions to sponsors who provide an investigational drug for treatment use either for intermediate-size patient populations or to larger populations under a treatment IND or protocol. Such sponsors would be able to recover costs associated with administering the program in addition to any direct costs.³⁴⁷ In all circumstances, sponsors would need to provide documentation showing that their cost calculations are consistent with the requirements of the regulation.³⁴⁸

³⁴² *Id.*; proposed 21 C.F.R. § 312.8(d).

³⁴³ *Id.*; proposed 21 C.F.R. § 312.8(d)(1).

³⁴⁴ *Id.* at 75172, 75181; proposed 21 C.F.R. § 312.8(d)(1)(i).

³⁴⁵ *Id.*; proposed 21 C.F.R. § 312.8(d)(1)(i).

³⁴⁶ *Id.*; proposed 21 C.F.R. § 312.8(d)(1)(i).

³⁴⁷ *Id.*; proposed 21 C.F.R. § 312.8(d)(2). These costs would include “the costs of monitoring the expanded access IND or protocol, complying with IND reporting requirements, and other administrative costs directly associated with the expanded access.” *Id.*

³⁴⁸ *Id.*; proposed 21 C.F.R. § 312.8(d)(3).

VI. CRITICISM OF FDA’S PROPOSAL: CEMENTING THE STATUS QUO

Despite some reports heralding FDA’s proposal as a victory for patient advocates and a major step forward in expanding access to investigational drugs³⁴⁹, the proposed changes to the regulatory scheme are unlikely to increase access. In fact, the proposed regulations generate disincentives to industry participation and create further regulatory barriers to patient access to expanded access programs.

FDA states that the purpose of the proposed regulations is to “increase awareness and knowledge of expanded access programs” and establish “clearly articulated procedures” for obtaining treatment through expanded access, as a result of which more patients with serious or immediately life-threatening diseases will get “the earliest possible access” to investigational therapies.³⁵⁰ But FDA has never been the major obstacle for patients seeking expanded access. Rather, patients are generally unable to obtain such drugs because manufacturers and drug developers lack the proper incentives to participate in expanded access programs.³⁵¹ Drug companies providing direct access to experimental therapies face increased challenges in enrolling clinical trials and may expose themselves to liability for any adverse events resulting from use of the unapproved drug. Adverse events occurring under an expanded access program could cause FDA to impose a clinical hold on ongoing investigations.³⁵² According to Steve Walker, co-founder of the Abigail Alliance, many pharmaceutical companies view expanded

³⁴⁹ See, e.g., “FDA to let dying have experimental drugs,” PHARMA MARKETLETTER, Jan. 23, 2007.

³⁵⁰ Proposed Rules to Expand Access, *supra* note 1, at 75149-75150.

³⁵¹ See George J. Ames, *Cancer and the Constitution*, 357 NEW ENG. J. MED.. 408-413 (Jul. 26, 2007).

³⁵² *Id.* But see “Pazdur’s Message: Don’t Fear Expanded Access Programs,” DRUG INDUSTRY DAILY, Mar. 13, 2008 (quoting Richard Pazdur, director of FDA’s Office of Oncology Drug Products, urging industry “not to fear retaliation from [FDA] when side effects from drugs are discovered under expanded access programs.”)

access programs as a “minefield that’s not worth the risk.”³⁵³ Even large pharmaceutical companies that do respond to patient petitions for access face pressure from activist groups to provide the drug free of charge because insurers rarely pay for experimental treatments.³⁵⁴

Industry disincentives are particularly palpable in the biotechnology sector, from which an enormous number of modern cancer therapies derive.³⁵⁵ Unlike traditional pharmaceutical companies, the biotechnology industry consists largely of young, small, privately held firms with few assets besides ideas and a patent. The road to producing a successful biotech product frequently spans between five and ten years and requires hundreds of millions of dollars.³⁵⁶ These start-ups rely on venture capital financing in which investors assume extremely high risks in exchange for the potential of exceptionally high rates of return,³⁵⁷ and most seek to license successful products to large pharmaceutical companies. Thus, such companies face enormous pressure to complete clinical trials and obtain an approved product.³⁵⁸

These financial disincentives to providing access are compounded by problems created from the often novel and non-traditional nature of biotechnology treatments. Consider Dendreon Corporation’s Provenge, a potential therapy for advanced, stage-4 prostate cancer. Provenge is a

³⁵³ Telephone Interview with Steve Walker, Co-Founder, Abigail Alliance for Better Access to Developmental Drugs (Apr. 4, 2008) (on file with author).

³⁵⁴ See Catherine Arnst, *Dying Patients Fight the FDA*, Business Week Online (July 26, 2007), http://www.businessweek.com/technology/content/jul2007/tc20070724_550192.htm

³⁵⁵ For background information on biotechnology, see generally John M. Golden, *Biotechnology, Technology Policy, and Patentability: Natural Products and Invention in the American System*, 50 EMORY L.J. 101 (Winter, 2001).

³⁵⁶ *Id.* at 118.

³⁵⁷ See Michael S. Mireles, *An Examination of Patents, Licensing, Research Tools, and the Tragedy of the Anticommons in Biotechnology Innovation*, 38 U. MICH. J.L. REFORM 141, 163 (2004). See also Mary Breen Smith, Comment, *An End to Gene Patents? The Human Genome Project Versus the United States Patent and Trademark Office’s 1999 Utility Guidelines*, 73 U. COLO. L. REV. 747, 758; STEPHEN C. BLOWERS, ET. AL, GUIDE TO THE IPO VALUE JOURNEY 284 (1999).

³⁵⁸ See, Mireles, *supra* note 357 at 164.

kind of cancer-fighting vaccine that primes the patient's immune system to fight tumors by combining the patient's own T-cells with prostatic acid phosphatase, a protein commonly found in prostate cancers.³⁵⁹ While traditional "pill in a bottle" type pharmaceuticals are characterized by low variable production costs, providing Provenge to a patient can cost the manufacturer as much as \$65,000 per year per patient.³⁶⁰

Prostate cancer causes approximately 30,000 deaths per year, and advanced stage-4 prostate cancer is nearly always fatal. In clinical trials, Provenge failed to stop the progression of the disease, but data demonstrated that patients receiving the drug survived approximately 4.5 months longer than patients receiving standard treatments.³⁶¹ In March 2007, an FDA advisory committee recommended the drug for approval,³⁶² but in May the agency withheld approval and ordered further clinical trials to provide additional data on the drug's effectiveness. A year later, these clinical trials have not yet been completed³⁶³ and terminally ill patients desperately continue to seek access to the drug.³⁶⁴

Dendreon has never been able to offer Provenge on an expanded access or compassionate use basis. Scientists at the advisory committee hearing last March, in response to calls from patient activists for quick approval of the drug, asked Dendreon to consider providing the drug for free on an expanded access basis.³⁶⁵ According to officers of the company, such a program

³⁵⁹ See Susan Todd, *Drugmakers race for cancer vaccines*, STAR-LEDGER (NEWARK, NEW JERSEY), Mar. 23, 2008. See also Arnst, *supra* note 354.

³⁶⁰ Telephone Interview with Rick Hamm, *supra* note 226.

³⁶¹ See Arnst, *supra* note 354; Telephone Interview with Rick Hamm, *supra* note 226.

³⁶² The advisory committee voted 17-0 that Provenge was safe for use and 13-4 that the drug was effective.

³⁶³ See *Provenge to See Early Results*, FDA NEW DRUG DAILY BULLETIN, Mar. 20, 2008.

³⁶⁴ See Arnst, *supra* note 354 (describing the Provenge "firestorm" resulting from FDA's decision to withhold approval. Prostate cancer activists and Dendreon investors have lobbied Congress, held demonstrations, and met with FDA Commissioner, Dr. Andrew von Eschenbach).

³⁶⁵ Telephone Interview with Rick Hamm, *supra* note 226.

would be impossible due to capacity constraints and the high cost of providing the drug. Rick Hamm, general counsel and a vice president at Dendreon, described the capacity constraints facing the company, noting that “for every patient we took on a compassionate use basis, it would mean one less patient we could take in a clinical trial,” thereby delaying approval of the drug.³⁶⁶ In addition to capacity, the “personalized” nature of the treatment generates enormous costs. Dendreon sustains considerable operating losses³⁶⁷ and must fight for every dollar it spends.³⁶⁸ Faced with the costs of “extremely expensive” clinical trials, personalized medicine, and a unique and complex antigen, in addition to major capacity constraints, Dendreon simply could not provide any access outside of fully enrolled clinical investigations.³⁶⁹

Dendreon’s experience is not unique, but FDA’s proposed rules fail to address the reality of biotech drug development. Indeed, the proposed rule for charging for investigational drugs creates new disincentives to industry participation. Proposed § 312.8 would allow drug sponsors to recover only “direct costs,” thereby excluding the vast majority of actual costs incurred,³⁷⁰ and narrows the class of recoverable costs available under current regulations. § 312.7(d) currently allows sponsors to recover costs of manufacture, research, development, and handling of an investigational drug,³⁷¹ but the new regulations would specifically eliminate research and development costs and would only allow recovery for administrative costs under a treatment protocol.

³⁶⁶ *Id.*

³⁶⁷ See 2006 DENDREON CORP. ANNUAL REPORT 32, *available at*: <http://www.dendreon.com> (from home page, follow link to “View the 2006 Annual Report.”) (noting accumulated deficit as of December 31, 2006 was \$392.4 million)

³⁶⁸ Telephone Interview with Rick Hamm, *supra* note 226. See also Angel Gonzalez, *Dendreon gathers \$47 million in stock sale*, SEATTLE TIMES, Apr. 4., 2008.

³⁶⁹ Gonzalez, *supra* note 368..

³⁷⁰ See Proposed Rules for Charging, *supra* note 2, at 75181; proposed 21 C.F.R. § 312.8(d)(1).

³⁷¹ 21 U.S.C. § 312.7(d)(3).

The proposal's decision to eliminate recovery of research and development costs substantially decreases existing industry incentives to participate in expanded access programs. Indeed, the potential to recover research and development costs has historically been the *only* economically sound reason to provide expanded access programs at all. The "direct costs" included in the proposed regulation represent a relatively insignificant percentage of drug development costs and, compared to the intense pressure to obtain speedy approval, would not provide sufficient incentive to risk the "minefield" of expanded access programs.³⁷² This disincentive exists even when the investigational compound consists of a small, relatively inexpensive molecule – let alone the expensive proteins typically developed by small biopharmaceutical companies.

The agency's concern that the present regulations are "not very specific and [do] not provide sufficient guidance to sponsors" about the kinds of costs that should be included likely derive from the inherent subjectivity surrounding "research and development" costs.³⁷³ FDA's concern stems from the fact that biotechnology firms that have yet to develop an approved drug typically possess nothing more than a potentially lucrative patent – virtually *all* of their costs could be considered research and development.³⁷⁴ Nonetheless, FDA could easily attempt to reduce the subjectivity inherent in research and development costs by delineating specific classes of acceptable R&D costs. For instance, FDA could specifically exclude the costs of drug discovery and product research while allowing a pro rata allocation of costs expended during clinical investigations of the drug. Specific guidance about recoverable costs would sufficiently

³⁷² Telephone Interview with Rick Hamm, *supra* note 226.

³⁷³ Proposed Rules for Charging, *supra* note 2, at 75169.

³⁷⁴ Telephone Interview with Rick Hamm, *supra* note 226.

rein in the subjective phrasing of “research and development” while continuing to provide a real and powerful incentive to provide expanded access.

While these proposed restrictions on charging reduce incentives for all drug manufacturers, they will particularly affect small biotechnology firms. While some firms might not ever be able to overcome preapproval capacity constraints, others undoubtedly would respond to real financial incentives to participate in expanded access programs. For instance, FDA could allow sponsors to allocate some fixed overhead costs of production on a pro rata basis. Many small companies could use the same facility to manufacture investigational treatments both for clinical trials and expanded access patients. Consider Vital Therapies, a small, biotechnology firm currently developing a liver failure treatment called ELAD. The treatment consists of “dialysis-like cartridges” grown through proprietary human liver cells and delivered to the patient through an “extracorporeal bedside unit.” After 16 years of development, the company is preparing to undertake Phase 3 trials. The product costs approximately \$25,000 per patient and, because the manufacturing processes represents new ground in cell culture development, the company cannot contract out production and must instead construct its own GMP manufacturing plant. Pro rata recovery of some of the significant capital investment and fixed manufacturing costs associated with such facilities would provide a real incentive for access to companies capable of overcoming capacity limitations.³⁷⁵

Although FDA’s proposed rules specifically acknowledge that current FDA procedures have not provided adequate access to patients, FDA nonetheless states explicitly that the “proposed rule largely clarifies current agency practice”³⁷⁶ and that the “fundamental problem

³⁷⁵ See Comments on Docket Nos. 2006N-061 and -0062, RIN 0910-AF13 and AF-14, Terry Winters, PhD & Kameron Maxwell PhD, Vital Therapies Hybrid Liver Therapy, (Jan. 30, 2007).

³⁷⁶ Proposed Rules on Charging, *supra* note 2, at 75177.

addressed by the proposed rule is one of incomplete information.”³⁷⁷ While the proposed rule does address the information problems raised by some patient advocates such as NCCS,³⁷⁸ others critics contend that the proposal merely codifies a failed agency policy, and worsens an access mechanism that has already proven unworkable in practice.³⁷⁹

In fact, the proposed regulation deviates from both statutory and current regulatory text in a number of ways that may restrict patient access to experimental drugs. For instance, § 561(c)(6) of the FD&C Act states that the criteria for obtaining a treatment use IND for a “serious” disease or condition consists of “sufficient” evidence of safety and effectiveness. Under current regulations, FDA specifically states in § 312.34(a) that, in the case of a serious disease, a drug will “ordinarily” be made available during phase 3 investigations, but in appropriate circumstances, may be made available during phase 2. Proposed § 312.320(a)(3)(i) would require stronger evidence than the current regulation and stronger evidence than compelled by FDAMA’s amendments to the FD&C Act, stating that in the case of a serious disease, “evidence would ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials....” The current regulations permit access during phase 2 trials, but the proposal would delay access until any phase 2 trials are complete. Further, the new regulation would require FDA to find phase 2 data to be “compelling” before approving access, a vague requirement inserted only to provide FDA with additional discretion to approve or refuse access as the agency sees fit. According to Mary Pendergast, former FDA Deputy Commissioner and Senior Adviser to the Commissioner, trial design limitations could easily

³⁷⁷ Proposed Rules to Expand Access, *supra* note 1, at 75157.

³⁷⁸ See NCCS Citizen Pet., *supra* note 218.

³⁷⁹ See Press Release, Abigail Alliance for Better Access to Developmental Drugs, FDA Release of Draft Regulations for Treatment Use and Charging for Investigational Drugs, (Dec. 13, 2006) (on file with author).

render many phase 2 trials not “compelling,” and FDA’s new proposal thus allows the agency to choose “to tie its hands” in making access available.³⁸⁰

The proposal’s safeguards to protect against interference with “the initiation, conduct, or completion of clinical investigations” or “otherwise compromise the potential development of the expanded access use” extends beyond the agency’s authority under FDAMA. Current § 312.34 does not address the impact of treatment use INDs on current or future clinical trials, but §561(c)(5) of the FD&C Act, as inserted by FDAMA in 1997, prohibits expanded access under a treatment IND that interferes “with the enrollment of patients in ongoing clinical investigations” under §§ 505(i) or 520(g) of the FD&C Act. The statute does not contemplate that FDA would consider the impact a treatment IND may have on *future* clinical investigations or “potential development” of the expanded use. Instead, FDA’s proposal goes beyond the agency’s statutory authority in order to provide additional discretion to approve or reject expanded access INDs.

FDA’s proposed rules for individual patient access also deviate sharply from Congress’ grant of authority in FDAMA. § 561(b) of the FD&C Act explicitly dictates that the patient’s licensed physician – not FDA – should evaluate the patient’s condition and determine whether any “comparable or satisfactory alternative therapy” is available for treatment. § 561(b) grants discretion to the patient’s physician to determine whether “the probable risk ...from the investigational drug...is not greater than the probable risk from the disease....” The proposed regulations, however, remove this discretion from the physician and instead gives authority to FDA, stating in § 312.305(a) that “FDA must determine that...there is no comparable or satisfactory alternative therapy to...treat the disease or condition” and that “FDA must determine

³⁸⁰ See Comment of Mary K. Pendergast, President, Pendergast Consulting, Docket No. 2006N-0062 and RIN 0910-AF14, Mar. 20, 2007 (on file with author).

that...[t]he potential patient benefit justifies the potential risks of the treatment and those potential risks are not unreasonable in the context of the disease or condition to be treated.”

The proposal not only removes discretion from physicians to the FDA, it also ratchets up the standard under which access to investigational drugs will be permitted. § 561(b)(1) of the FD&C Act states that the FDA should compare the risk of treatment to the risk of disease, but under proposed § 312.305(a)(2) FDA will compare whether the potential patient benefit justifies the risk, and further that those risks are not unreasonable. In her comment to the FDA, Mary Pendergast notes that § 561(b) does not invite FDA to undertake a “reasonableness” determination by authorizing a licensed physician to compare the risks of the treatment to the risks of the disease.³⁸¹ The agency’s decision to reserve this authority for itself serves only to impose an additional regulatory barrier between patient and physician and will not contribute to increased patient access.

FDA’s proposal also fails to address drug sponsors’ concerns about adverse events occurring during expanded access programs. Drug sponsors frequently refuse to participate in single-patient IND programs out of fear that adverse events in a single-patient trial will weigh heavily against approval of the drug upon eventual submission of an NDA.³⁸² Patients seeking single-patient INDs have often progressed to a later stage of disease than those enrolled in clinical trials – they are frequently sicker, have exhausted all other options, may well have additional illnesses, and may have taken other medications or have other factors rendering them

³⁸¹ *Id.* at 5-6. (Noting that although § 506(b)(2) of the FD&C Act allows FDA to determine whether there is “sufficient” evidence of safety and effectiveness to support use of an investigational drug, that section is embedded in another part of the law and “does not empower a risk determination”).

³⁸² *Id.* at 9.

particularly vulnerable to adverse events.³⁸³ FDA should specifically address manufacturers' concerns about adverse events under such INDs and allow sponsors to separately report such events to FDA in the eventual NDA. The proposal gives no indication that FDA will treat adverse effects under single-patient INDs any differently than effects occurring in controlled clinical investigations, and the agency's failure to address these concerns will only bolster industry resistance to expanded access.

The Abigail Alliance maintains that patient access will only increase if FDA commits itself to modernizing the clinical trials process and adapting its regulatory regime to the changing needs of modern science. Dr. Scott Gottlieb, former FDA Deputy Commissioner for Medical and Scientific Affairs, shares this view and has argued that neither court rulings nor legislative action will successfully expand access unless FDA adopts better science and a modern approach to clinical investigation.³⁸⁴ Noting that the proposed rules merely “codif[y] what the agency is already doing,” he notes that FDA “already has robust authorities to speed certain drugs to market” but fails to make use of them, in some cases because the agency lacks the ability to “advance scientific principles that would enable faster approvals.”³⁸⁵

Indeed, despite substantial increases in biomedical research and scientific breakthroughs in our understanding of disease, the number of new drugs in the pharmaceutical pipeline is shrinking,³⁸⁶ and despite increased numbers of oncology drugs entering clinical trials, the

³⁸³ *Id.*

³⁸⁴ See Rebecca Mashaw, *FDA's system for access to unapproved drugs broken, but experts question if Congress or 'Abigail' will help*, BIORESEARCH COMPLIANCE REPORT, Mar. 1, 2007 at 1.

³⁸⁵ *Id.*

³⁸⁶ See, e.g., FOOD AND DRUG ADMIN., INNOVATION STAGNATION, CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS (2004) *available at* <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>; see also UNITED STATES

regulatory path has grown longer and more expensive than ever before.³⁸⁷ As FDA has itself acknowledged in its report on the Critical Path Initiative, “[t]he medical product development process is no longer able to keep pace with basic scientific innovation.”³⁸⁸ Steve Walker of the Abigail Alliance agrees, arguing that FDA’s refusal to depart from clinical trial methodology based on statistics derived from randomized, double-blind, placebo-controlled studies hampers development of modern oncology drugs.³⁸⁹ Clinical trial methodology has largely crystallized in the fifty years since the Drug Amendment of 1962, and FDA’s continued reliance on outdated endpoints and statistical analysis may obscure the potential of modern cancer treatments and impose unnecessary delays in approval.³⁹⁰

FDA’s Critical Path Initiative is intended to address these concerns. Announced in 2004, the initiative is FDA’s effort to modernize the science through which FDA evaluates the way regulated products are developed and manufactured. In its 2004 white paper, “Innovation Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products,” FDA acknowledged the decrease in recent innovative medical products submitted for FDA approval, the rising costs of clinical development, and the high proportion of products that fail in late clinical trials. The report called for a concerted effort to modernize scientific tools and better harness the potential of bioinformation used to evaluate safety and effectiveness in new medical

GOVERNMENT ACCOUNTABILITY OFFICE, NEW DRUG DEVELOPMENT, REPORT GAO-07-49, (2006).

³⁸⁷ See, DR. RICHARD A. MILLER, M.D., IMPACT OF FDA REGULATION ON ONCOLOGY DRUG RESEARCH AND DEVELOPMENT (Mar. 14, 2008) *available at* http://www.aei.org/docLib/20080314_MillerPaper1.pdf

³⁸⁸ See FOOD AND DRUG ADMIN., INNOVATION STAGNATION, CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS, *supra* note 386 at ii.

³⁸⁹ Telephone Interview with Steve Walker, *supra* note 353.

³⁹⁰ *Id.* See also MILLER, *supra* note 387 at 8-9.

products.³⁹¹ In 2006, FDA announced a “Critical Path Opportunities List,” in which the agency identified needs for modernization among various areas along the critical path of development.³⁹² The Opportunities List proposes further research into “innovative” clinical trial design, including active control trials, enrichment designs (in which a sub-class of patients likely to experience a particularly high response rate are studied), and trial designs built upon accumulated prior experience or information.³⁹³

While the Critical Path Initiative offers a glimmer of hope for modernization at FDA, four years after its announcement the Initiative remains little more than a list of ideas on the agency’s website. In November 2007, FDA announced the Clinical Trials Transformation Initiative (CTTI) in a Memorandum of Understanding for Public Private Partnership with Duke University.³⁹⁴ Although only recently announced, CTTI appears unlikely to generate major changes in the clinical trial system. The press release announcing the initiative’s formation states that it will explore ways to establish national standards of research, alternative models for Institutional Review Boards, accreditation for clinical research professionals, and greater use of technology for data management.³⁹⁵

VII. CONCLUSION

³⁹¹ See FOOD AND DRUG ADMIN., FDA’S CRITICAL PATH INITIATIVE – SCIENCE ENHANCING THE HEALTH AND WELL-BEING OF ALL AMERICANS, <http://www.fda.gov/oc/initiatives/criticalpath/initiative.html>.

³⁹² See FOOD AND DRUG ADMIN., CRITICAL PATH OPPORTUNITIES LIST, http://www.fda.gov/oc/initiatives/criticalpath/reports/opp_list.pdf.

³⁹³ *Id.* at 8. The list also describes increased use of multiple endpoints and various methods of measuring patient response.

³⁹⁴ See Memorandum of Understanding Between the Food and Drug Administration and Duke University, 72 Fed. Reg. 65745 (Nov. 23, 2007); *see also* Clinical Trials Transformation Initiative, <http://www.fda.gov/oc/initiatives/criticalpath/clinicaltrials.html>.

³⁹⁵ Press Release, FDA, FDA and Duke Launch Public-Private Partnership to Modernize Clinical Trials (Nov. 26, 2007), *available at* <http://www.fda.gov/oc/initiatives/criticalpath/partnership.html>.

FDA's proposed rules are likely to decrease patient access to investigational therapies. Under increased pressure from patient activism, proposed legislation, and constitutional litigation, FDA has tactically announced this proposal in an effort to maintain control of clinical investigations and risk/benefit analysis of patient welfare while superficially addressing the concerns of critics and terminally ill patients who seek greater autonomy and control over their treatment options. The proposal largely codifies existing pathways to expanded access, but grants FDA greater discretion to approve or reject applications than current regulations provide, and, in removing the ability to recover research and development costs, eliminates the primary financial incentive for industry participation in expanded access programs. Until FDA commits itself to truly improving the science of clinical trials and acknowledges the fundamentally different risk analysis facing terminally ill patients, such patients will remain frustrated in their attempts to obtain access to investigational therapies.